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(71) Applicant *(for all designated States except US)*: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 5th floor, 1111 Franklin Street, Oakland, CA 94607-5200 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BEADLE, James, R.** [US/US]; 11723 Petenwell Road, San Diego, CA 92131 (US). **HOSTETLER, Karl** [US/US]; 14024 Rue St. Raphael, Del Mar, CA 92014 (US).

(74) Agent: **RIEGER, Dale, L.**; Fish & Richardson P.C., 12390 El Camino Real, San Diego, CA 92130 (US).

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(54) Title: METHODS FOR PREPARATION OF NUCLEOSIDE PHOSPHONATE ESTERS

(57) Abstract: A process is provided for the preparation of lipophilic monoesters of formula (3) and their stereoisomers. The process includes the steps of esterification of a phosphonate with a lipophilic alcohol, then allowing the resultant product to react with a suitably protected nucleoside in the presence of a strong base. In certain embodiments, the process is used for the preparation of alkyl or alkoxyalkyl lipid ether monoesters of nucleoside phosphonates which are useful as antiviral, anticancer or antiparasitic agents.

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METHODS FOR PREPARATION OF NUCLEOSIDE PHOSPHONATE ESTERS

RELATED APPLICATION DATA

This application claims priority to U.S. provisional applications Serial Nos. 60/550,402, filed March 4, 2004, entitled "Methods for Preparation of Nucleoside Phosphonate Esters" and 60/567,198 filed April 30, 2004, entitled " Methods for Preparation of Nucleoside Phosphonate Esters" to James R. Beadle and Karl Hostetler. The disclosure of the above referenced applications is incorporated by reference herein.

FIELD

Provided herein are processes for the preparation of lipophilic monoesters of phosphonate compounds. In one embodiment, the processes are for the preparation of nucleoside phosphonate monoesters.

BACKGROUND

Acyclic nucleoside phosphonates are broad spectrum antiviral agents. One example is (*S*)-1-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine, (cidofovir, CDV). CDV has been reported to be active against all double stranded DNA viruses. It has also been reported that the in vitro activity of long chain alkoxyalkyl esters of CDV, for example hexadecyloxypropyl-CDV (HDP-CDV) and octadecyloxypropyl CDV, (ODE-CDV) against herpes group viruses (HCMV and HSV), orthopoxviruses (vaccinia and cowpox) and others is increased when compared to unmodified CDV. These alkoxyalkyl esters of CDV have been shown to have good oral bioavailability. Oral administration of the alkoxyalkyl analogs provides decreased exposure to the kidneys versus when unmodified drug is given intravenously. This is expected to improve tolerance to drug exposure. Preliminary studies in lethal ectromelia, cowpox and vaccinia virus challenge in mice indicate that HDP-CDV and ODE-CDV are effective in preventing death when given orally. CDV itself is not effective orally. In addition to CDV derivatives, the in vitro antiviral activity and oral bioavailability of many other nucleoside phosphonates such as 9-(2-phosphonomethoxyethyl)-guanine (PMEG), 9-(2-phosphonomethoxyethyl)adenine (PMEA, adefovir), and

(S)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine ((S)-HPMPA), (R)-9-(2-phosphonomethoxypropyl)adenine (PMPA, tenofovir), and 9-(phosphonopropoxymethyl)guanine (PPMG) can be improved by derivitazation with a lipophilic group.

Several procedures for the preparation of nucleoside phosphonate monoesters have been reported in the literature. Alkylation of cyclic cidofovir (cCDV) using alkoxyalkyl bromides followed by basic hydrolysis is known in the art. However, this approach gave very poor yields of product and required difficult isolation procedures because regioisomers are formed. For example, cyclic cidofovir (N,N'-dicyclohexyl 4-morpholinecarboxamidine salt) on treatment with 3-alkoxy-1-bromoalkanes (N,N-DMF, 80 °C) gives esters of cCDV (See, Beadle *et al.*, Antimicrobial Agents and Chemotherapy 46(8), 2381-2386, *2002* and Kern *et al.*, Antimicrobial Agents and Chemotherapy 46(4), 991-995, *2002*) The yields in this reaction are low and careful chromatography is required to avoid contamination with N-dialkylated compound. Holý obtained the esters of 9-(2-phosphonomethoxyethyl)adenine (PMEA) by treating PMEA with triphosgene in N,N-DMF followed by reaction with the desired alcohol in good yields. However, triphosgene is highly toxic and its use is not desirable. Other methods for making phosphonate esters have been reported in the literature, for example, Armilli, in U.S. Patent No. 5,717,095, describes several procedures for preparing cCDV esters; Jasko *et al.*, (Bioorganicheskaya Khimiya 20(1), 50-54, *1994*) used the ethyl ester of toluenesulphonyloxymethyl-phosphonate to prepare 5'-O-phosphonomethyl derivatives of nucleosides; and Saady *et al.*, in Synlett (6), 643-644, *1995,* used tetrafluoroboronic acid and triphenyl phosphene. Further methods for making phosphonate monoesters are provided by Holy *et al.,* Collection of Czechoslovak Chemical Communications 59(8), 1853-1869, *1994;* Starrett, *et al.* in EP 0481214; and Holy, Synthesis (4), 381-385, *1998 describe other methods*. The synthetic methods reported in the literature result in low yields and involve difficult isolation steps.

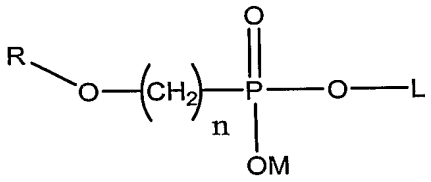
There is, therefore, a continuing need for processes for the manufacture of lipophilic esters of nucleoside phosphonates.

SUMMARY

In certain embodiments, provided herein are processes for the preparation of lipophilic esters of nucleoside phosphonate monoesters. In certain

embodiments, the processes provided herein are for preparing the lipophilic monoesters of antiviral and anticancer nucleoside phosphonates. In certain embodiments, the processes provided herein include the steps of providing a lipophilic phosphonate monoester; reacting the lipophilic phosphonate monoester with an antiviral nucleoside or antiproliferative nucleoside having a free –OH group; and isolating the lipophilic phosphonate monoester of the antiviral nucleoside or antiproliferative nucleoside.

In one embodiment, the process is for the preparation of lipophilic nucleoside phosphonate monoesters of formula 3, including their stereoisomers,



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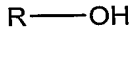
wherein the process includes the steps of

a) providing compounds of formula 1 and formula 2;

b) reacting, the compound of formula 1 and the compound of formula 2 in an aprotic solvent in presence of a strong base; and



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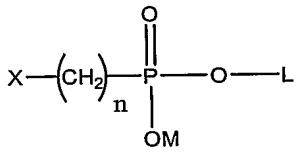

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c) isolating the compound of formula 3;

wherein M is –H, or a physiologically acceptable monovalent cation;

L is a lipophilic group; R is a nucleoside or a pharmaceutically acceptable derivative thereof; X is a leaving group; n is 1 to 3. In one embodiment, n is 1.

In certain embodiments, the reactive sites in the nucleosides for use in the processes provided herein can be protected by suitable protecting groups known in the art. The protecting groups can be then removed by deprotection reactions known in the art. Certain of the antiviral and anticancer nucleoside phosphonates that can be prepared using the processes provided herein are described by Hostetler *et al.* in International Patent Application No. WO 01/39721.

In one embodiment, the processess provided herein give lipophilic nucleoside phosphonate monoesters in high purity and good yields within a commercially feasible amount of time in a minimum number of process steps. In certain embodiments, the processes provided herein do not need difficult separation processes in the preparation of lipophilic esters of nucleoside phosphonate monoesters.

In certain embodiments, provided herein are lipophilic phosphonate monoesters of formula 1 used in the processes provided herein.

DETAILED DESCRIPTION

A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

The term "nucleoside" as used herein, refers to a molecule composed of a heterocyclic base and a carbohydrate. Typically, a nucleoside is composed of a heterocyclic nitrogenous base in N-glycosidic linkage with a sugar. Nucleosides are recognized in the art to include natural bases (standard), and non-natural bases well known in the art. The carbohydrates include the true sugars found in natural nucleosides or a species replacing the ribofuranosyl moiety or acyclic sugars. The heterocyclic nitrogenous bases are generally located at the 1' position of a nucleoside sugar moiety. Nucleosides generally contain a base and sugar group. The nucleosides can be unmodified or modified at the sugar, and/or base moiety, (also referred to interchangeably as nucleoside analogs, modified nucleosides, non-natural nucleosides, non-standard nucleosides; see for example, Eckstein *et al.*, International PCT Publication No. WO 92/07065 and Usman *et al.*, International PCT Publication No. WO 93/15187). In natural nucleosides the heterocyclic base is typically thymine, uracil, cytosine, adenine or guanine. In certain embodiments, acyclic sugars contain 3-6 carbon atoms and include, for example, the acyclic sugar moieties present in acyclovir (-CH_2-O-CH_2 CH_2-OH), ganciclovir (-CH_2-O-CH(CH_2OH)-CH_2-OH), and the like. Natural nucleosides have the β-D-configuration. The term "nucleoside" shall be understood to

encompass unnatural configurations and species replacing the true sugar that lack an anomeric carbon. In natural nucleosides the heterocyclic base is attached to the carbohydrate through a carbon-nitrogen bond. The term "nucleoside" shall be understood to encompass species wherein the heterocyclic base and carbohydrate are attached through a carbon-carbon bond (C-nucleosides).

Where the nucleoside contains 1 or more functional groups that may be reactive to form undesired products under the reaction conditions of the present process, for example, the amino groups of cytosine and adenine and the 2-amino and 4-oxo groups of guanine, such functional groups may be blocked using the protecting groups commonly employed in nucleoside chemistry. For example, the amino group of adenine and cytosine may be protected by benzoyl; the 4-oxo and 2-amino groups of guanine may be protected by the triphenylmethyl (trityl) group. The selection of methods for introducing and subsequent removal of such protecting groups are well known to one of ordinary skill in the pertinent art.

As used herein, the terms "lipophilic" or "long-chain" refer to the cyclic, branched or straight chain chemical groups that when covalently linked to a phosphonic acid to form a phosphonate monoester increase oral bioavailability and enhance activity of the nucleoside phosphonates as compared with the parent nucleoside phosphonates. These lipophilic groups include, but are not limited to alkyl, alkoxyalkyl, and alkylglyceryl.

The terms "nucleoside phosphonate" and "acyclic nucleoside phosphonate" refer to the group of phosphonomethoxyalkyl or phosphono substituted nucleoside derivatives that are biologically active, for example, as anti-viral, anti-cancer or anti-parasitic drugs.

The term "methylene phosphonate" refers to compounds of the formula $X\text{-}CH_2\text{-}P(O)(OH)_2$ and their addition salts where X is a leaving group such as toluenesulfonyloxy, methylsulfonyloxy, bromo- or iodo, etc.

As used herein, the term "lipophilic monoesters of nucleoside phosphonates" refers to compound where a lipophilic group is covalently attached to a nucleoside phosphonate via an ester linkage.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known

methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, nitrates, borates, methanesulfonates, benzenesulfonates, toluenesulfonates, salts of mineral acids, such as but not limited to hydrochlorides, hydrobromides, hydroiodides and sulfates; and salts of organic acids, such as but not limited to acetates, trifluoroacetates, maleates, oxalates, lactates, malates, tartrates, citrates, benzoates, salicylates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=C(OR) where R is hydrogen, alkyl, alkenyl, alkynyl, and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C(OC(O)R) where R is hydrogen, alkyl, alkenyl, alkynyl, or cycloalkyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

As used herein, a prodrug is a compound that, upon in vivo administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic

processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392). Other prodrugs for use herein are described elsewhere herein.

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. It is understood that the present invention encompasses any racemic, optically active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possesses the useful properties described herein, it being well known in the art how to prepare optically active forms and how to determine antiproliferative activity using the standard tests described herein, or using other similar tests which are well known in the art.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

As used herein, the term "alkyl" refers to a monovalent straight or branched chain or cyclic radical. In certain embodiments, the alkyl group contains from one to twenty-four carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl, octadecyl, nonadecyl,

eicosyl, 18-methyl-nonadecyl, 19-methyl-eicosyl, and the like. As used herein lower alkyl refers to alkyl groups of 1 to 6 carbon atoms.

As used herein, "substituted alkyl" refers to alkyl groups further bearing one or more substituents, including, but not limited to substituents selected from lower alkyl, hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, trifluoromethyl, cyano,azido, nitro, nitrone, amino, amido, -C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, and sulfuryl, which may be protected or unprotected as necessary, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Second Ed. 1991, hereby incorporated by reference.

As used herein, "alkenyl" refers to straight or branched chain hydrocarbon group having one or more carbon-carbon double bonds. In certain embodiments, the alkenyl group contains from 2 up to 24 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As used herein, "alkynyl" refers to straight or branched chain hydrocarbon group having one or more carbon-carbon triple bonds. In certain embodiments, the alkynyl group contains from 2 up to 24 carbon atoms, and "substituted alkynyl" refers to alkynyl groups further bearing one or more substituents as set forth above.

As used herein, "aryl" refers to aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted aryl" refers to aryl groups further bearing one or more substituents as set forth above.

As used herein, "heteroaryl" refers to aromatic groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heteroaryl" refers to heteroaryl groups further bearing one or more substituents as set forth above.

As used herein “subject” is an animal, typically a mammal, including human, such as a patient.

The phrase "effective amount" as used herein means an amount required for prevention, treatment, or amelioration of one or more of the symptoms of

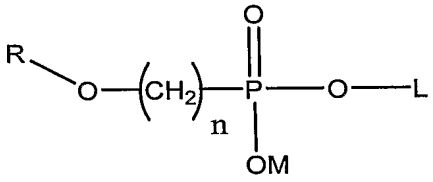
diseases or disorders associated including those associated with viral infection, parasitic infections and cell proliferation.

Where the number of any given substituent is not specified (e.g., haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem. 11*:942-944).

B. Processes

In certain embodiments, provided herein is a process for making lipophilic nucleoside phosphonate monoesters of formula 3, including their stereoisomers,



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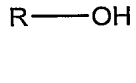
wherein the process includes the steps of

a) providing compounds of formula 1 and formula 2;

b) reacting, the compound of formula 1 and the compound of formula 2 in an aprotic solvent in presence of a strong base; and



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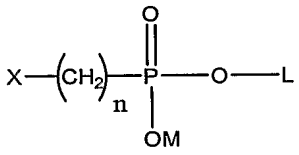

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c) isolating the compound of formula 3;

wherein M is –H, or a physiologically acceptable monovalent cation;

L is a lipophilic group; R is a nucleoside or a pharmaceutically acceptable derivative thereof; X is a leaving group; and n is 1 to 3. In one embodiment, n is 1.

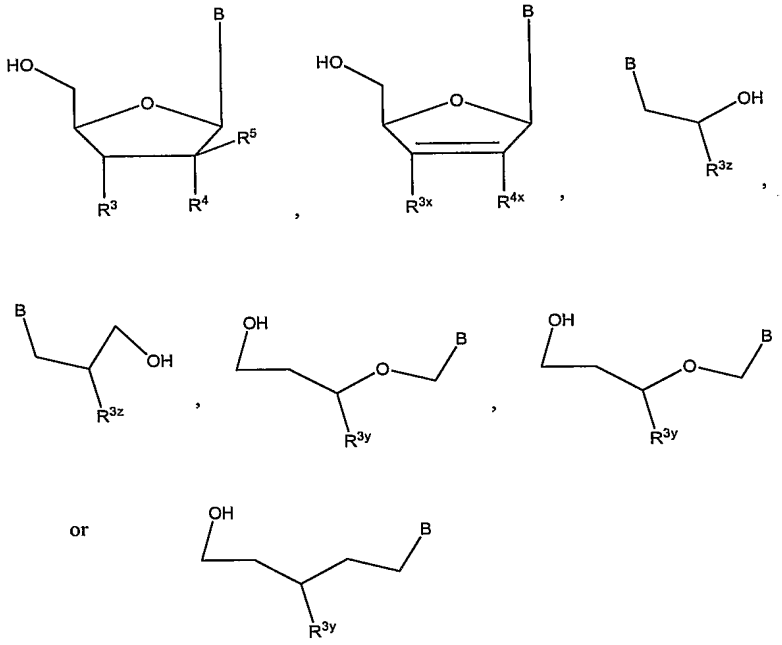
A variety of aprotic solvents known to those of skill in the art can be used in the process. Exemplary aprotic solvents include, but are not limited to N,N-

dimethylformamide (N,N-DMF), tetrahydrofuran (THF) and triethyamine. The reaction can be carried out in presence of a variety of strong bases known in the art, such as sodium hydride, potassium t-butoxide and others.

In certain embodiments, X is selected from halogen, toluenesulfonyloxy, and methylsulfonyloxy. In certain embodiments, X is bromo or iodo. In certain embodiments, X is toluenesulfonyloxy.

In certain embodiments, M is –H, Na^+, K^+, or NH_4^+. In other embodiments, M is –H or Na^+. In other embodiments, M is –H. In other embodiments, M is Na^+.

In certain embodiments, the compounds of formula 2 in the processes provided herein have formula:



wherein

R^3, R^4 and R^5 are each independently H, hydroxy, halo, azido, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

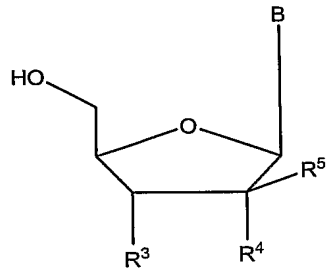
B is a purine or pyrimidine base or analog thereof;

R^{3x} is H, azido, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl or substituted or unsubstituted C_{2-6} alkynyl;

R^{4x} is H, C_{1-6} substituted or unsubstituted alkyl, C_{2-6} substituted or unsubstituted alkenyl or C_{2-6} substituted or unsubstituted alkynyl; and

R^{3z} is H, C_{1-6} alkyl, hydroxylC_{1-6} alkyl, haloC_{1-6} alkyl, azidoC_{1-6} alkyl or OH.

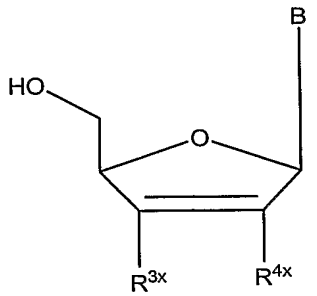
In certain embodiments, the compounds of formula 2 in the processes provided herein have formula:



wherein the variables are as described elsewhere herein.

In certain embodiments, R^3 is H, azido, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl or substituted or unsubstituted C_{2-6} alkynyl. In certain embodiments, R^3 is H, azido, substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^3 is H or azido. In certain embodiments, R^3 is azido. In certain embodiments, R^3 is H. In certain embodiments, R^4 and R^5 are each independently selected from hydrogen, halo and hydroxyalkyl. In certain embodiments, R^4 and R^5 are each independently selected from halo and hydroxyalkyl. In certain embodiments, R^4 and R^5 are each independently selected from fluoro and hydroxymethyl. In certain embodiments, R^4 is selected from fluoro and hydroxymethyl. In certain embodiments, R^5 is selected from fluoro and hydroxymethyl.

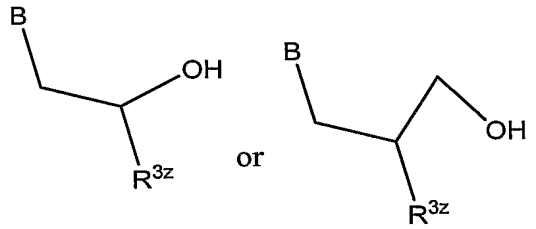
In certain embodiments, the compounds of formula 2 in the processes provided herein have formula:



wherein the variables are as described elsewhere herein.

In certain embodiments, R^{3x} is H, azido, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl or substituted or unsubstituted C_{2-6} alkynyl; R^{4x} is H, C_{1-6} substituted or unsubstituted alkyl, C_{2-6} substituted or unsubstituted alkenyl or C_{2-6} substituted or unsubstituted alkynyl and other variables are as defined elsewhere herein. In certain embodiments, R^{3x} is H, azido or substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{4x} is H, C_{1-6} substituted or unsubstituted alkyl, C_{2-6} substituted or unsubstituted alkenyl or C_{2-6} substituted or unsubstituted alkynyl. In certain embodiments, R^{4x} is H, or C_{1-6} alkyl.

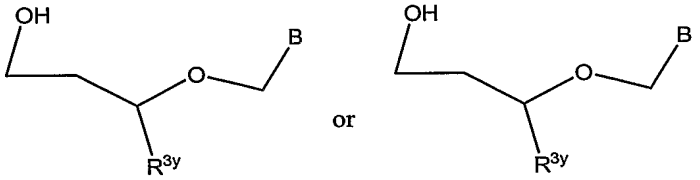
In certain embodiments, the compounds of formula 2 in the processes provided herein have formula:



wherein the variables are as described elsewhere herein.

In certain embodiments, R^{3z} is H, C_{1-6} alkyl, hydroxyl C_{1-6} alkyl, halo C_{1-6} alkyl, azido C_{1-6} alkyl or OH and the other variables are as defined elsewhere herein. In certain embodiments, R^{3z} is hydrogen C_{1-6} alkyl or hydroxyl C_{1-6} alkyl. In certain embodiments, R^{3z} is hydrogen or hydroxy methyl. In certain embodiments, R^{3z} is hydroxy methyl. Optionally, the OH groups are protected, for example as an ester or an ether. In certain embodiments, R^{3z} may be in S or R configuration.

In certain embodiments, the compounds of formula 2 in the processes provided herein have formula:

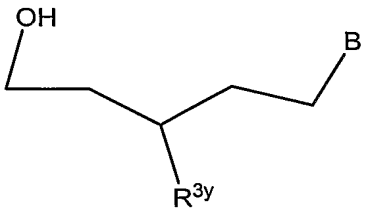


wherein the variables are as described elsewhere herein.

In certain embodiments, R^{3y} is H, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl or substituted or unsubstituted C_{2-6} alkynyl; or OH and the other variables are as defined elsewhere herein. In certain

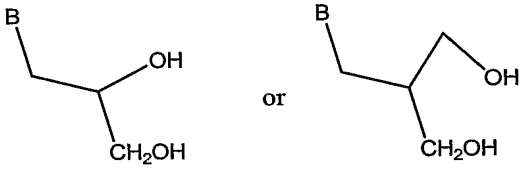
embodiments, R^{3y} is hydrogen C_{1-6} alkyl or hydroxyl C_{1-6} alkyl. In certain embodiments, R^{3y} is hydrogen or hydroxy methyl. In certain embodiments, R^{3y} may be in S or R configuration.

In certain embodiments, the compounds of formula 2 in the processes provided herein have formula:

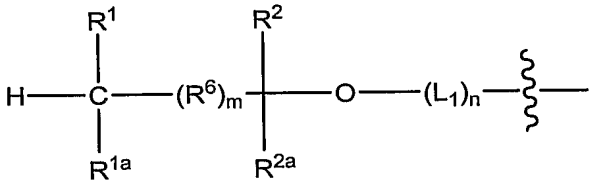


wherein the variables are as described elsewhere herein.

In certain embodiments, the compounds of formula 2 in the processes provided herein have formula:



In certain embodiments, L is a substituted or unsubstituted C_8-C_{24} alkyl or substituted or unsubstituted C_8-C_{24} alkenyl having from 1 to 6 double bonds, wherein substituents when present are selected from one or more halogen, alkyl, -OH, -SH, cycloalkyl, or epoxide; or L has formula:

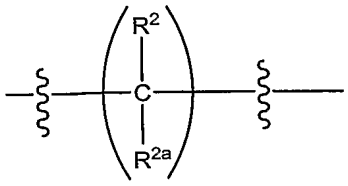


wherein:

R^1 and R^{1a} are independently –H, optionally substituted –O(C_1-C_{24})alkyl, -O(C_1-C_{24})alkenyl, -O(C_1-C_{24})acyl, -S(C_1-C_{24})alkyl, -S(C_1-C_{24})alkenyl, or –S(C_1-C_{24})acyl, wherein at least one of R^1 and R^{1a} are not –H, and wherein the alkenyl or acyl moieties optionally have 1 to 6 double bonds,

R^2 and R^{2a} are independently –H, optionally substituted-O(C_1-C_7)alkyl, -O(C_1-C_7)alkenyl, -S(C_1-C_7)alkyl, -S(C_1-C_7)alkenyl, -O(C_1-C_7)acyl, -S(C_1-C_7)acyl, -N(C_1-C_7)acyl, -NH(C_1-C_7)alkyl, -N((C_1-C_7)alkyl)$_2$, oxo, halogen, -NH_2, -OH, or –SH;

R^6, when present, is:



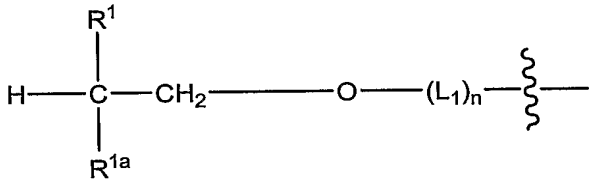
L_1 is a valence bond or a bifunctional linking molecule of the formula –J-$(CR^7R^7)_t$-G-, wherein t is an integer from 1 to 24, J and G are independently –O-, -S-, -C(O)O-, or –NH-, and R^7 is –H, substituted or unsubstituted alkyl, or alkenyl;

m is an integer from 0 to 6; and

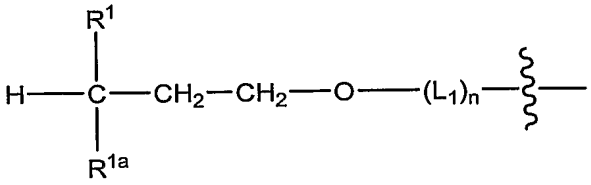
n is 0 or 1.

In certain embodiments, m = 0, 1 or 2. In certain embodiments, m = 0 or 1. In certain embodiments, m = 0. In certain embodiments, m = 1. In certain embodiments, R^2 and R^{2a} are H.

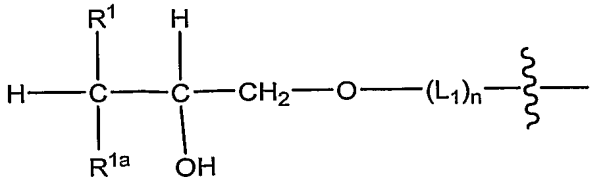
In certain embodiments, L has formula:



wherein R^1, R^{1a}, and L_1, and n are as defined elsewhere herein.



In certain embodiments, L has formula:



wherein R^1, R^{1a}, and L_1, and n are as defined elsewhere herein.

In certain embodiments, L is hexadecyloxypropyl, octadecyloxypropyl, or octadecyloxyethyl.

In certain embodiments, the glycerol residue has the $-(L_1)_n-$ moiety joined at the *sn*-3 position of glycerol. In certain embodiments, the glycerol residue has the $-(L_1)_n-$ moiety joined at the *sn*-1 position of glycerol.

In certain embodiments, R^1 is an alkoxy group having the formula $-O-(CH_2)_t-CH_3$ wherein t is 0-24. In other embodiments, t is 8, 10, 12, 13, 14, 15, 16, 17, 18, 19 or 20. In other embodiments, t is 13, 14, 15, 16, 17, 18, 19 or 20. In other embodiments, t is 15, 16, 17, 18, 19 or 20. In other embodiments, t is 17, 18, 19 or 20. In other embodiments, t is 15 or 17.

In certain embodiments, L is a substituted or unsubstituted C_8-C_{24} alkyl, substituted or unsubstituted C_8-C_{24} alkenyl having from 1 to 6 double bonds or substituted or unsubstituted C_8-C_{24} alkynyl having from 1 to 6 triple bonds, wherein substituents when present are selected from one or more halogen, alkyl, $-OR^w$, $-SR^w$, cycloalkyl or epoxide, where R^w is hydrogen or alkyl and where the alkyl, alkenyl, alkynyl groups may be further substituted or unsubstituted.

In certain embodiments, L is an alkyl, alkenyl or alkynyl group and contains 8, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 carbon atoms and can be straight or branched chain moieties. In certain embodiments, L is a C_{16}-C_{23} straight or branched chain alkyl or C_{16}-C_{23} straight or branched chain alkenyl. In other embodiments, L is a C_{17}-C_{19} straight or branched chain alkyl or C_{17}-C_{19} straight or branched chain alkenyl. In other embodiments, L is C_{17}-alkyl, C_{18}-alkyl or C_{19} alkyl. In other embodiments, L is C_{17}-alkenyl, C_{18}-alkenyl or C_{19} alkenyl. In other embodiments, L is C_{17}-C_{22} alkyl. In other embodiments, L is C_{17} alkyl, C_{18} alkyl, C_{19} alkyl, C_{20} alkyl, C_{21} alkyl, or C_{22} alkyl.

In certain embodiments, L is substituted with one or more groups selected from lower alkyl and halo. In certain embodiments, L is substituted with one or more methyl groups. In certain embodiments, L is substituted with one or more fluoro groups. In certain embodiments, L is C_{16}-C_{23} alkyl and is substituted with one or more methyl or fluoro groups. In certain embodiments, the methyl group or the fluoro group substituent is present on the penultimate carbon of the alkyl, alkenyl, or alkynyl chain. In certain embodiments, the L is 7-methyl-octyl, 8-methyl-nonyl, 9-methyl-decyl, 10-methyl-undecyl, 11-methyl-dodecyl, 12-methyl-tridecyl, 13-methyl-tetradecyl, 14-methyl-pentadecyl, 15-methyl-

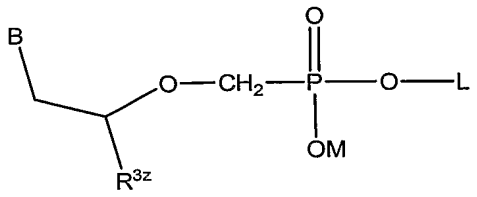
hexadecyl, 16-methyl-heptadecyl, 17-methyl-octadecyl, 18-methyl-nonadecyl, 19-methyl-eicosyl, 20-methyl-heneicosyl, 21-methyl-docosyl, 22-methyl-tricosyl, 7-fluoro-octyl, 8- fluoro-nonyl, 9- fluoro-decyl, 10- fluoro-undecyl, 11- fluoro-dodecyl, 12- fluoro-tridecyl, 13-fluoro-tetradecyl, 14- fluoro-pentadecyl, 15- fluoro -hexadecyl, 16- fluoro-heptadecyl, 17- fluoro-octadecyl, 18- fluoro-nonadecyl, 19- fluoro-eicosyl, 20- fluoro-heneicosyl, 21- fluoro-docosyl or 22-fluoro-tricosyl.

In certain embodiments, L is selected from alkyl, alkenyl and alkynyl groups that contain 8, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 carbon atoms and can be straight or branched chain moieties. In certain embodiments, the L group is a C_{16}-C_{23} straight or branched chain alkyl or C_{16}-C_{23} straight or branched chain alkenyl. In other embodiments, L is a C_{17}-C_{19} straight or branched chain alkyl or C_{17}-C_{19} straight or branched chain alkenyl. In other embodiments, L is C_{17}-alkyl, C_{18}-alkyl or C_{19} alkyl. In other embodiments, L is C_{17}-alkenyl, C_{18}-alkenyl or C_{19} alkenyl. In other embodiments, L is C_{17}-C_{22} alkyl. In other embodiments, L is C_{17} alkyl, C_{18} alkyl, C_{19} alkyl, C_{20} alkyl, C_{21} alkyl, or C_{22} alkyl.

In certain embodiments, L is C_{16}-C_{23} alkyl that is substituted with one or more groups selected from lower alkyl and halo. In certain embodiments, L is substituted with one or more methyl groups. In certain embodiments, L is substituted with one or more fluoro groups. In certain embodiments, L is C_{16}-C_{23} alkyl and is substituted with one or more methyl or fluoro groups. In certain embodiments, the methyl group or the fluoro group substituent is present on the penultimate carbon of the alkyl, alkenyl, or alkynyl chain. In certain embodiments, the L is 7-methyl-octyl, 8-methyl-nonyl, 9-methyl-decyl, 10-methyl-undecyl, 11-methyl-dodecyl, 12-methyl-tridecyl, 13-methyl-tetradecyl, 14-methyl-pentadecyl, 15-methyl-hexadecyl, 16-methyl-heptadecyl, 17-methyl-octadecyl, 18-methyl-nonadecyl, 19-methyl-eicosyl, 20-methyl-heneicosyl, 21-methyl-docosyl, 22-methyl-tricosyl, 7-fluoro-octyl, 8- fluoro-nonyl, 9- fluoro-decyl, 10- fluoro-undecyl, 11- fluoro-dodecyl, 12- fluoro-tridecyl, 13-fluoro-tetradecyl, 14- fluoro-pentadecyl, 15- fluoro -hexadecyl, 16- fluoro-heptadecyl, 17- fluoro-octadecyl, 18- fluoro-nonadecyl, 19- fluoro-eicosyl, 20- fluoro-heneicosyl, 21- fluoro-docosyl or 22- fluoro-tricosyl.

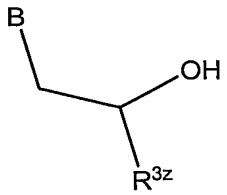
In certain embodiments, B is selected from a natural or non natural purine or pyrimidine base. In certain embodiments, the base is selected from pyrimidin-1-yl, pyrimidin-3-yl, purin-3-yl, purin-7-yl or purin-9-yl residue. In certain embodiments, the base is thymin-1-yl, cytosine-1-yl, adenine-9-yl or guanine-9-yl.

In certain embodiments, provided herein is a process for making lipophilic nucleoside phosphonate monoesters of formula **6**, including their stereoisomers,

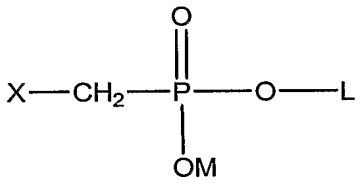


6

including the steps of reacting a compound of formula **4** and a compound of formula **5** in presence of a strong base;



4



5

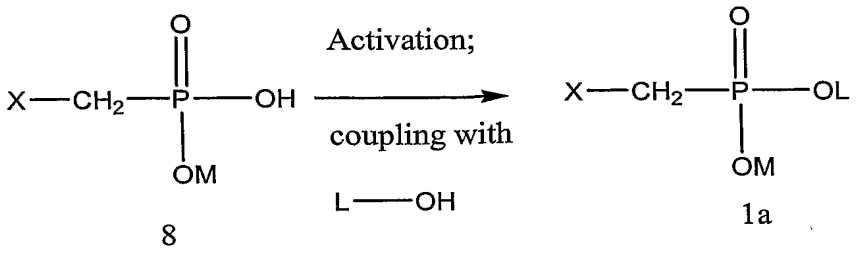
and isolating the compound of formula **6**;

wherein the variables are as described elsewhere herein. In certain embodiments, R^{3z} is hydrogen, methyl or hydroxymethyl.

Synthesis of lipophilic methylene phosphonate monoesters

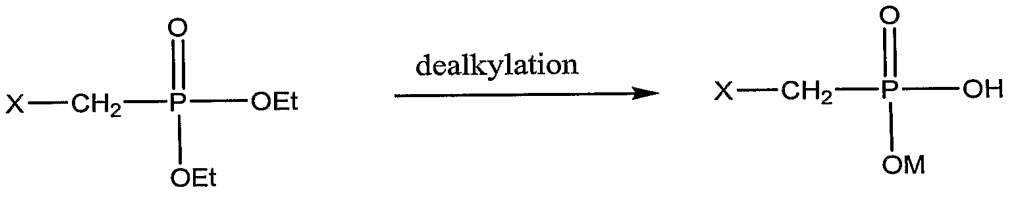
In certain embodiments, the processes provided herein include a step of preparing the methylene phosphonate lipophilic monoesters of formula 1. The preparation of compound of formula 1, in some embodiments, include the steps of activation of phosphonic acid by reaction with an activating agent, such as thionyl chloride or oxalyl chloride followed by coupling with a lipophilic alcohol of formula L-OH. In certain embodiments, the coupling reaction is carried out using condensation reactions known in the art including, but not limited to coupling in presence of N,N-dicyclohexylcarbodiimide (DCC); 1,1-carbonyldiimidazole (CDI); 2,4,6-triisopropylbenzenesulfonyl chloride (TIPS-

Cl); trichloroacetonitrile; alkylation with alkyl halide; Mitsunobo alkylation (diethylazodicarboxylate/ triphenylphosphine).



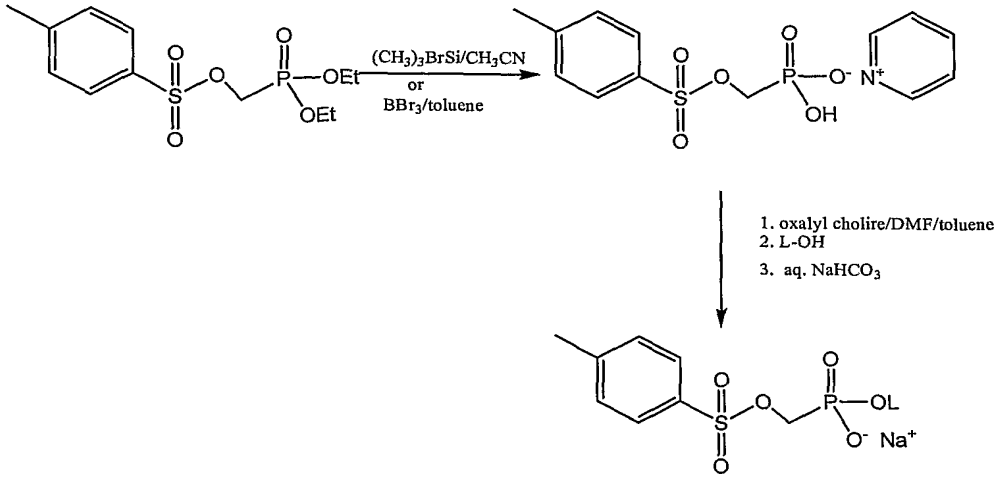
8 1a

In certain embodiments, the compound of formula 8 is obtained from the dialkyl esters of phosphonic acid by dealkylating the alkyl groups, as shown in an exemplary reaction with diethyl ester of formula **9a**. The dealkylation reaction conditions are known in the art.

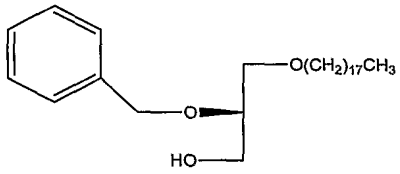


9a

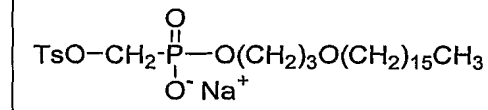
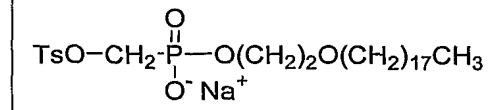
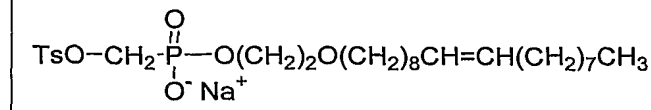
In certain embodiments, the compound of formula **9a** is diethyl p-toluenesulfonyloxymethylphosphonate. Diethyl p-toluenesulfonyloxy-methylphosphonate can be prepared by methods known in the art, such as by treatment of diethyl hydroxymethylphosphonate (commercially available) with p-toluenesulfonyl chloride, in the presence of a base. The diester is treated with halotrialkylsilane, such as bromotrimethylsilane or boron trihalide, such as boron tribromide to cleave both ethyl groups. The resulting p-toluenesulfonyloxy-methyl phosphonic acid is conveniently isolated as the crystalline pyridinium salt or used as a free acid. The phosphonic acid is then activated by reaction with oxalyl chloride (catalyzed by N,N-DMF); followed by treatment with a desired lipophilic alcohol. After hydrolysis, (aqueous $NaHCO_3$) the esters are isolated as the sodium salts.

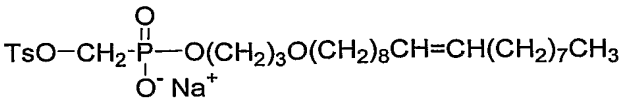
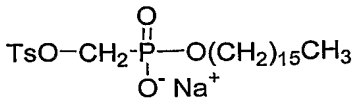
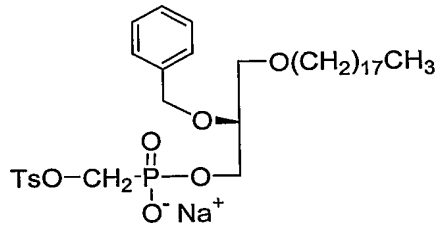


Exemplary lipophilic alcohols for use include, but are not limited to $CH_3(CH_2)_{15}O(CH_2)_3OH$; $CH_3(CH_2)_{17}O(CH_2)_2OH$; $CH_3(CH_2)_7CH{=}CH(CH_2)_8O(CH_2)_2OH$; $CH_3(CH_2)_{15}OH$ $CH_3(CH_2)_7CH{=}CH(CH_2)_8O(CH_2)_3OH$; and

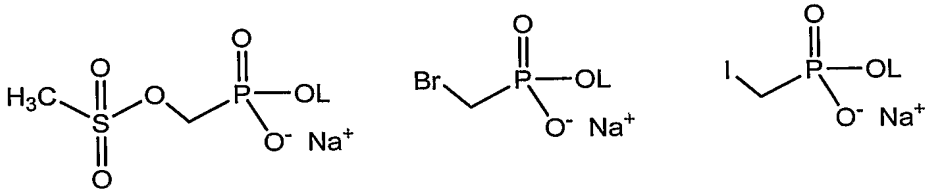


Exemplary methylene phosphonate monoesters for use herein are provided in Table 1 below:

Lipid alcohol used:	**Structure of resulting methylene phosphonate monoester:**
3-hexadecyloxy-1-propanol	
2-octadecyloxy-1-ethanol	
2-oleyloxy-1-ethanol	

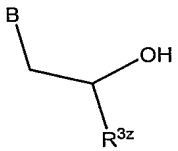
3-oleyloxy-1-propanol	
1-hexadecanol	
1-*O*-octadecyl-2-*O*-benzyl-*sn*-glycerol	

Exemplary methylene phosphonate monoesters with various leaving groups for use herein are provided below:

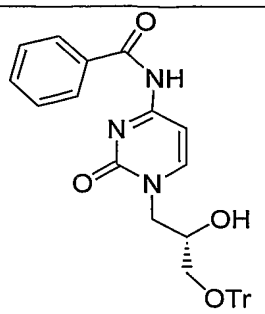
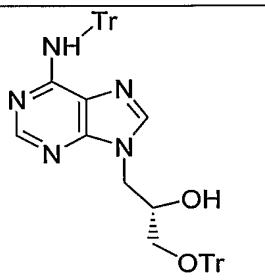
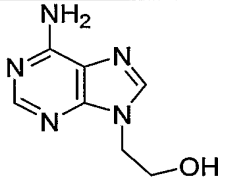
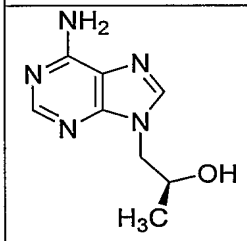
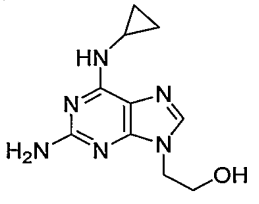


Synthesis of N-substituted derivatives of heterocyclic bases

In certain embodiments, the methods provided herein are used for the preparation of lipophilic esters of acyclic nucleoside phosphonates. The starting compounds for these reactions, for example, hydroxyalkyl derivatives of purine and pyrimidine bases are prepared by methods known in the art. Exemplary acyclic nucleosides that can be derivatized to lipophilic monoesters of phosphonates according to the methods provided herein are shown below in Table 2. In certain embodiments, the acyclic nucleosides have general formula:



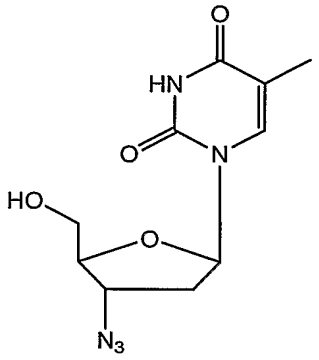
where the variables are as described in Table 2. In the compounds in Table 2, the OH on R^{3z} substituent, when present, is protected by a trityl group.

Cmpound	B	R^{3z}	reference
	N^4-benzoyl-cytosin-1-yl-	$-CH_2OH$	**A practical synthesis of (S)-HPMPC.** Brodfuehrer, Paul R.; Howell, Henry G.; Sapino, Chester, Jr.; Vemishetti, Purushotham Tetrahedron Letters (1994), 35(20), 3243-6 **Preparation of hydroxyphosphonomethoxypropyl nucleosides.** Vemishetti, Purushotham; Brodfuehrer, Paul R.; Howell, Henry G.; Sapino, Chester, Jr. (Bristol-Myers Squibb Co., USA). PCT Int. Appl. (1992), 43 pp. WO 9202511 A1 19920220
	N^6-trityl-adenin-9-yl-	$-CH_2OH$	**The bis-trityl route to (S)-HPMPA.** Webb, Robert R. II. Nucleosides & Nucleotides (1989), 8(4), 619-24. **A convenient synthesis of S-HPMPA [(S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine].** Webb, Robert R., II; Martin, John C. Tetrahedron Letters (1987), 28(42), 4963-4
	Adenine-9-yl	-H	**Method and cyclic carbonates for nucleotide analogs.** Bischofberger, Norbert W.; Kent, Kenneth M. US 5514798 A 19960507
	Adenine-9-yl	$-CH_3$	**Preparation of antiretroviral enantiomeric nucleotide analogs.** Holy, Antonin; Dvorakova, Hana; Declercq, Erik Desire Alice; Balzarini, Jan Marie Rene. PCT Int. Appl. (1994), 96 pp. WO 9403467 A2
	N^6-cyclopropyl-adenin-1-yl	-H	

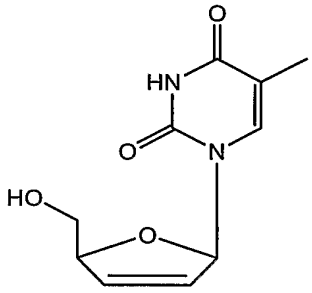
In one embodiment N^4-monomethoxytriyl-$O^{3'}$-(trityl)-dihydroxypropylcytosine or N^4,$O^{3'}$-ditrityl-dihydroxypropylcytosine are prepared as intermediates in the synthesis of cidofovir monoesters.

In certain embodiments, the antiviral nucleosides that can be derived according to the process provided herein have free 5′-hydroxy group. Some non-limiting exemplary nucleosides are provided below:

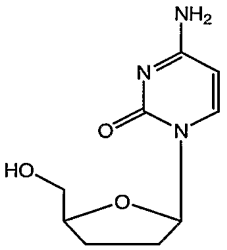
3′-azido-3′,5′-dideoxythymidine (AZT)
Hakimelahi, G. et al.



3′,5′-dideoxythymidine-2′-ene (d4T)
Ibid.

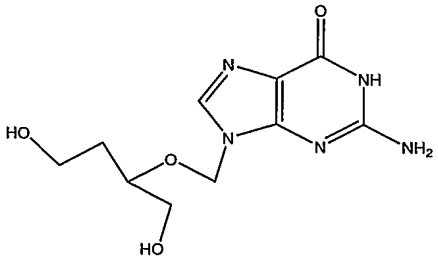


2′,3′-dideoxycytidine (ddC)
Kofoed, T., et al.

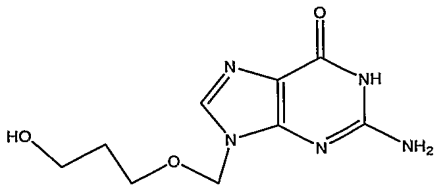


Further examples of antiviral nucleosides include:

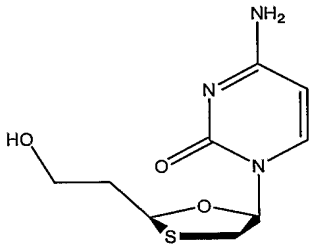
Ganciclovir
Huffman, et al.



Acyclovir
Ibid.



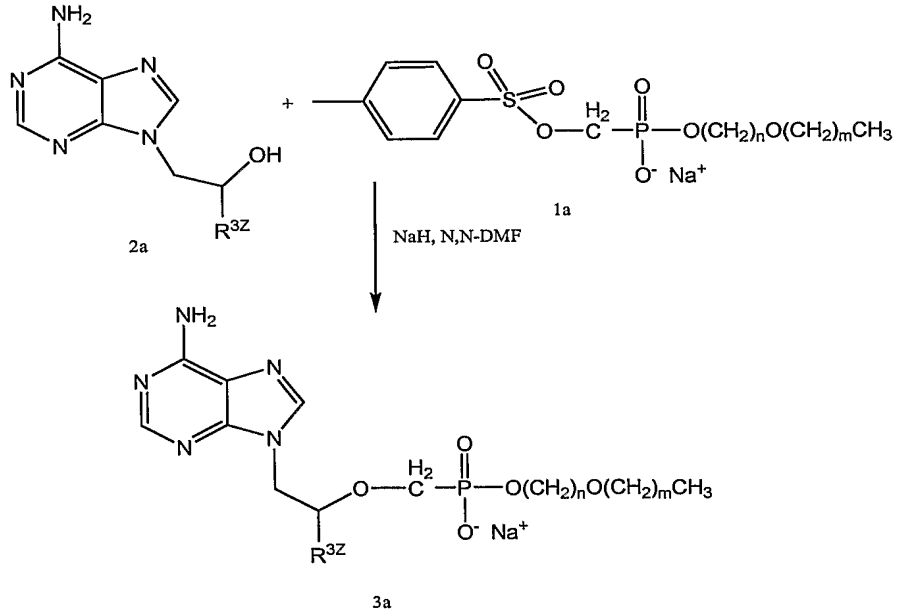
3'-thia-2',3'-
dideoxycytidine
Kraus, , et al.



In other embodiments, antiviral nucleosides for use in the processes provided herein include ddA, ddI, ddG, L-FMAU, DXG, DAPD, L-dA, L-dI, L-(d)T, L-dC, L-dG, FTC, penciclovir, and the like.

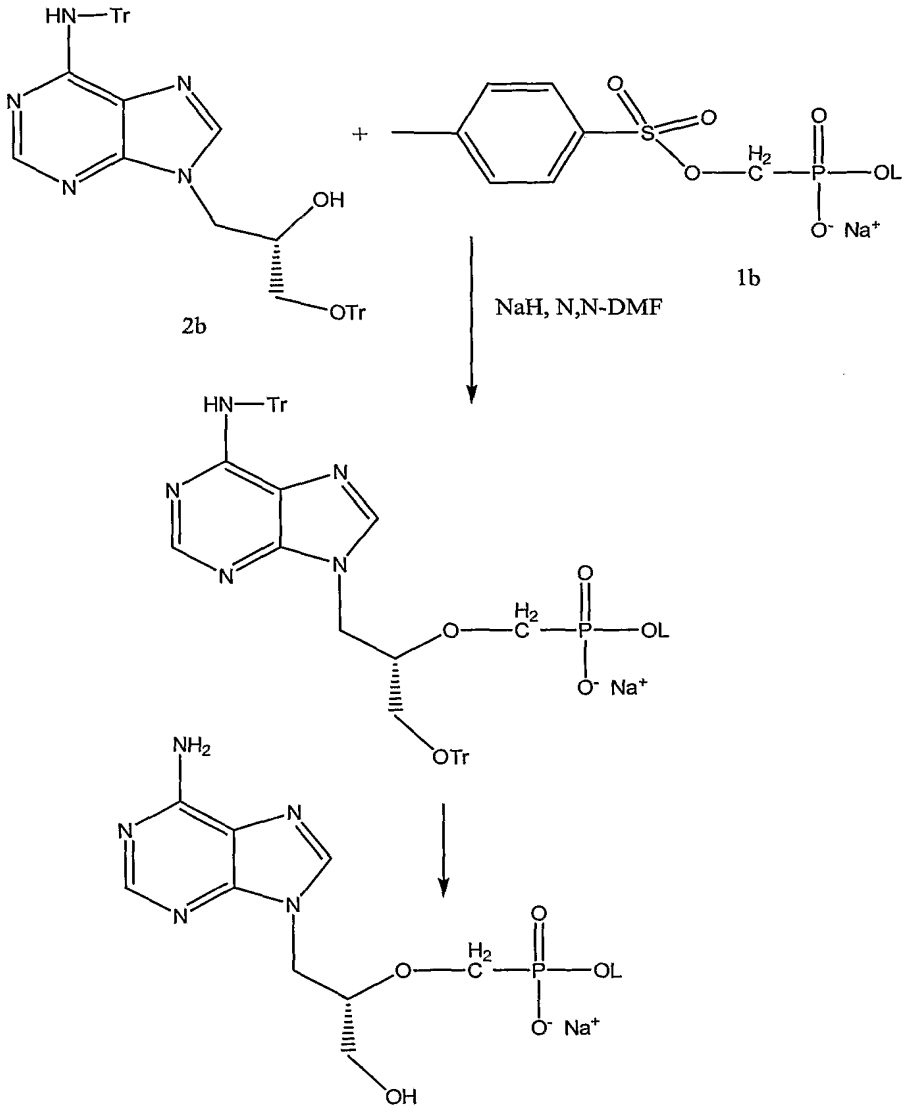
Exemplary processes for the preparation of alkoxyalkyl esters of adefovir, tenofovir, HPMPA and PMPMG are illustrated in the reactions below:

i) Alkoxyalkyl esters of adefovir and tenofovir



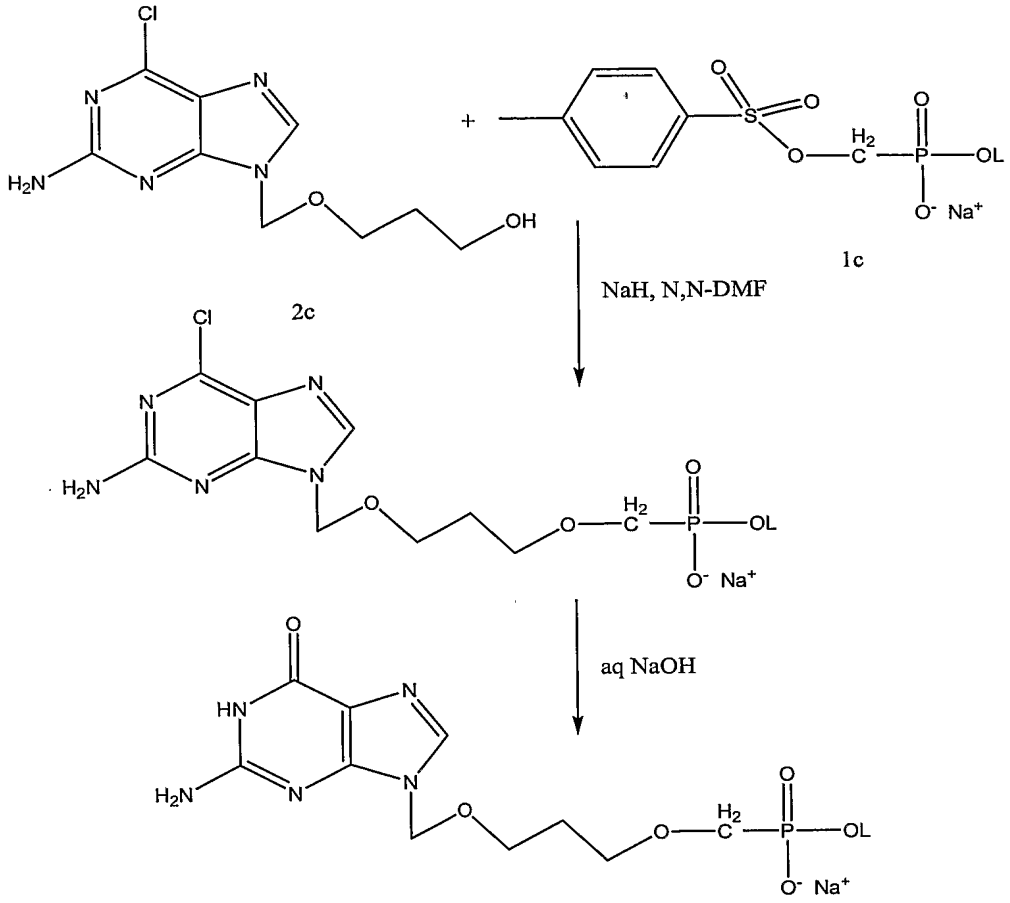
2a 1a 3a

ii) Alkoxyalkyl esters of HPMPA



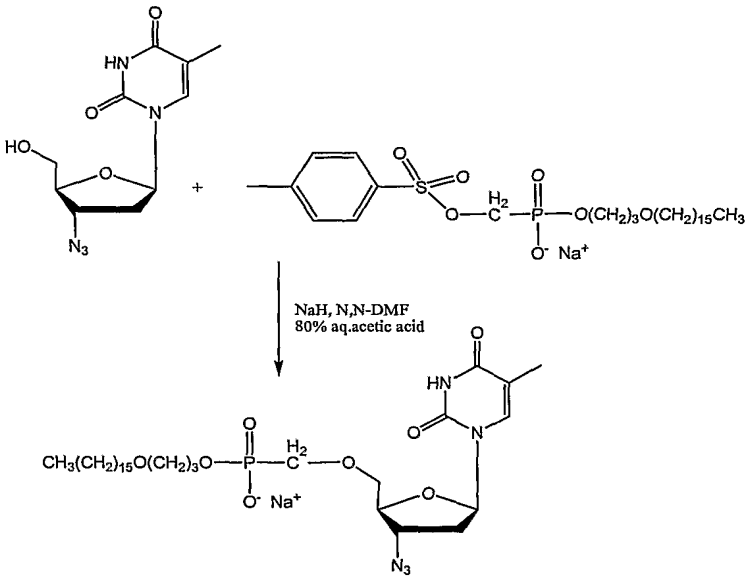
3b

iii) Alkoxyalkyl esters of PMPMG



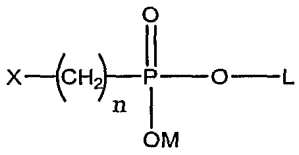
Exemplary processes for the synthesis of hexadecyloxypropyl-5′-phosphonomethyl AZT is illustrated in the reaction scheme below:

Synthesis of Hexadecyloxypropyl-5′-phosphonomethyl-AZT



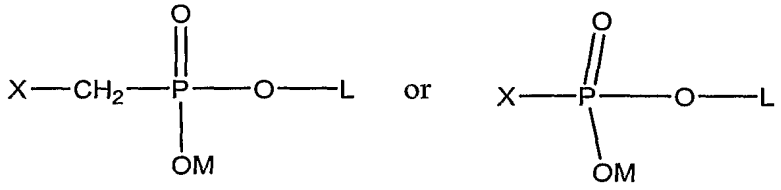
C. Compounds

In certain embodiments, provided herein are compounds of formula:



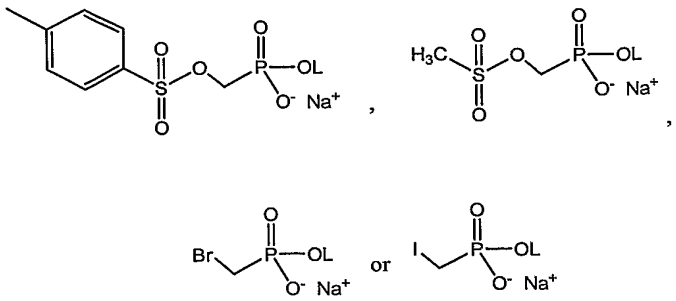
wherein the variables are described elsewhere herein.

In one embodiment, the compound has formula:



wherein the variables are described elsewhere herein.

In one embodiment, the compound has formula:



wherein the variables are described elsewhere herein.

In one embodiment, provided herein is a compound selected from N^4-monomethoxytrityl-$O^{3'}$-(trityl)-dihydroxypropylcytosine and N^4,$O^{3'}$-ditrityl-dihydroxypropylcytosine.

In certain embodiments, the compounds prepared by the methods provided herein are useful for the prevention, or amelioration one or more symptoms of diseases associated with viral infections, including, but not limited to influenza; hepatitis B and C virus; cytomegalovirus (CMV); herpes infections, such as those caused by Varicella zoster virus, Herpes simplex virus types 1 & 2, Epstein-Barr virus, Herpes type 6 (HHV-6) and type 8 (HHV-8); Varicella zoster virus infections such as shingles or chicken pox; Epstein Barr virus infections, including, but not limited to infectious mononucleosis/glandular; retroviral infections including, but not limited to SIV, HIV-1 and HIV-2; ebola virus; adenovirus and papilloma virus. In certain embodiments, the disease is drug resistant hepatitis B.

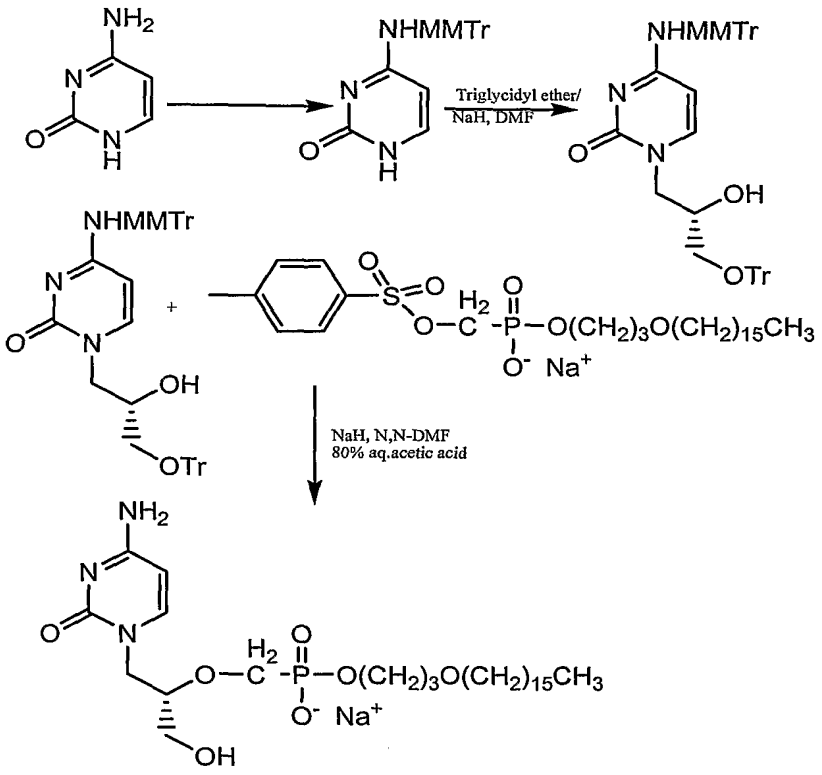
The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLES

The isolation and purification of the compounds and intermediates described in the examples can be effected, if desired, by any suitable separation or purification procedure such as , for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick layer preparative chromatography, distillation, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures are in the examples below. Other equivalent separation or isolation procedures can of course also be used.

EXAMPLE 1: Synthesis of Hexadecyloxypropyl- cidofovir

SCHEME



1. Synthesis of N^4-(trityl)cytosine

Cytosine (25.0 g, 225 mmol) was suspended in dry pyridine (500 mL) and stirred at room temperature. N,O-bis(trimethylsilyl)acetamide (114.0 g, 562 mmol) was added dropwise over 20 min., then the mixture was stirred 2 hours until the cytosine dissolved and a clear solution was obtained. Trityl chloride (75.0 g, 269 mmol) was added and stirring continued 5 hours. The mixture was filtered and the filtrate was evaporated in vacuo. The residue from the filtrate was adsorbed on silica gel and purified by flash chromatography on silica gel (gradient 100% CH_2Cl_2 to 10% EtOH/ CH_2Cl_2). The solvent was evaporated to give a white solid (1.6 g, 2% yield) ^1H NMR: ($CDCl_3$ + CD_3OD) δ 5.74 (d, 1H), 6.07 (s, 1H), 7.10-7.42 (m, 15H), 8.27 (d, 1H), 10.18 (s, 1H).

2. Synthesis of N^4-(monomethoxytrityl)cytosine

Prepared by a method known in the art. A mixture of cytosine (20 g, 0.18 mol) and monomethoxytrityl chloride (70 g, 0.23 mol) was suspended in dry

pyridine (750 mL). Triethylamine (25 mL, 0.18 mol) was added to the mixture in one portion. The mixture was heated gently (40 °C) and stirred overnight. Water (150 mL) was added to the stirred suspension, followed by dichloromethane (150 mL). The resulting precipitate was collected by vacuum filtration (8 g). The filtrate was evaporated and the residue was triturated with a mixture of water and dichloromethane. A second crop of product (35 g) was obtained. The total yield was 43 g (62%), m.p. 264-265°C decomp., m.p.lit. 255-258 °C.

3. Synthesis of N^4, $O^{3'}$-bis(trityl)-dihydroxypropylcytosine

N^4-tritylcytosine (0.5 g, 1.4 mmol) and (S)-trityl glycidyl ether (0.5 g, 1.6 mmol) were stirred in dry N,N-DMF. Potassium t-butoxide (50 mg, 0.55 mmol) was added and the mixture was heated to 100 °C for 4 hours. After cooling, the reaction mixture was added to ice water. The solid was collected by filtration and dried under vacuum. The crude product was adsorbed on silica gel and purified by flash column chromatography (gradient 100% hexanes/0% ethyl acetate to 0% hexanes/ 100% ethyl acetate). Fractions were evaporated give a white solid (960 mg, 100% yield). ^{1}H NMR: ($CDCl_3$) δ 7.15-7.34 (m, 30H), 6.79 (br s, 1H), 6.72 (d, 1H), 4.84 (d, 1H), 4.36 (d, 1H) 4.13 (d,1H), 4.07 (br s, 1H), 3.69 (dd, 1H), 3.25 (dd, 1H), 2.97 (d, 1H).

4. Synthesis of N^4-monomethoxytrityl-$O^{3'}$-trityl-dihydroxy-propylcytosine

A mixture of N^4-monomethoxytritylcytosine (3.44 g, 8.9 mmol) and sodium hydride (0.043 g, 1.78 mmol) in dry N,N-DMF (50 mL) was stirred at room temperature for 1 hr. (S)-Trityl glycidyl ether (2.5 g, 8.0 mmol) was added to the mixture and it was stirred at 105 °C for 7 hours. The mixture was allowed to cool to room temperature. N,N-DMF was evaporated. The residue was dissolved in chloroform (200 mL) and washed with water (2 x 20 mL). The chloroform layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel to give 5.0 g of product (89%), mp 144 -154 °C, ^{1}H NMR ($CDCl_3$): δ 7.37- 7.13 (m, 25H); 7.11 (d, J=9Hz, 2H); 6.84 (d, J=9Hz, 2H); 6.80 (br s, 1H); 6.77 (d, J=7Hz, 1H); 4.87 (d, J=7Hz, 1H); 4.47 (d, J=4Hz, 1H); 4.18 (dd, J= 12 and 6 Hz, 1H); 4.10 (br s, 1H); 3.80 (s, 3H); 3.72 (dd, J= 14 and 6 Hz, 1H); 3.27 (dd, J= 9 and 4 Hz, 1H); 2.95 (dd, J= 10 and 8 Hz, 1H).

5. Synthesis of pyridinium toluenesulfonyloxymethylphosphonate

Diethyl toluenesulfonyloxymethylphosphonate (1.0 g, 3.1 mmol) was dissolved in dry CH_3CN (25 mL) and the mixture was cooled in an ice bath and stirred magnetically. Bromotrimethylsilane (1.42 g, 9.3 mmol) was added all at once. The mixture was stirred for 4 hours. The solvent was evaporated to leave a thick oil. MeOH/pyridine (30 mL) was added and the mixture was stirred 30 min. The solvent was evaporated and the residue was combined with p-dioxane and stirred. White crystals were collected and recrystallized from EtOH to yield 750 mg product (73% yield).

6. Synthesis of toluenesulfonyloxymethylphosphonate, hexadecyloxypropyl ester (HDP-TsOMPA)

To a solution of pyridinium toluenesulfonyloxymethylphosphonate (1.0 g, 3.0 mmol) in dry toluene (20 mL) was added oxalyl chloride (0.39 mL, 4.5 mmol) and N,N-DMF (0.02 mL, 0.3 mmol) in one portion. The solution was stirred at room temperature for 1 hour. Toluene and the excess oxalyl chloride were removed under vacuum. The residue was redissolved in toluene (10 mL). 3-Hexadecyloxy-1-propanol (0.81 g, 2.7 mmol) was added. The mixture was stirred at room temperature overnight. Triethyl ammonium hydrogen carbonate buffer (10 mL) was added to the mixture which was stirred for 30 min. Solvents were evaporated. The residue was dissolved in $CHCl_3$ (50 mL), washed with water (2 x 10 mL) and the solvent evaporated to give 1 gram of crude product. The impurities were removed by flash column chromatography (silica gel, 15% EtOH/CH_2Cl_2) Yield = 0.60 g (40%). ^{1}H NMR: ($CDCl_3$) δ 0.88 (t, 3H), 1.25 (br s, 26H), 1.46 (m,2H), 1.71 (p, 2H), 2.46 (s, 3H), 3.34 (t, 2H), 3.80 (dd, 2H), 3.98 (d, 2H), 7.37 (d, 2H), 7.76 (d, 2H).

7. Synthesis of N^4-monomethoxytrityl-$O^{3'}$-trityl-cidofovir, hexacecyloxypropyl ester

Sodium hydride (0.14 g, 6.0 mmol) was added to a solution of N^4-monomethoxytrityl-$O^{3'}$-trityl-dihydroxypropylcytosine (0.70 g, 1.0 mmol) in dry N,N-DMF (10 mL). Toluenesulfonyloxymethylphosphonate, hexadecyloxypropyl ester (0.82 g, 1.05 mmol) was then added to the solution. The mixture was stirred at 70 °C for 24 hours and then cooled to room temperature. $CHCl_3$ (60 mL) and water (10 mL) were added to the mixture, which then was stirred for 5-10 min.

The organic layer was washed with water (2 × 10 mL), dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel to give 0.47 g of **N^4-monomethoxytrityl-$O^{3'}$-trityl-cidofovir, hexadecyloxypropyl ester** (47%). ^1H NMR ($CDCl_3$ + CD_3OD): δ 7.39-7.37 (m, 6H); 7.31-7.29 (m, 6H); 7.24-7.22 (m, 7H); 7.20-7.15 (m, 6H); 7.08 (d, J=9Hz, 2H); 6.82 (d, J=9Hz, 2H); 6.70 (d, J=7Hz, 1H); 4.82 (d, J=8Hz, 1H); 4.20-4.05 (m, 1H); 3.95-3.85 (m, 2H); 3.80 (s, 3H); 3.75-3.62 (m,2H); 3.43-3.35 (m, 2H); 3.35-3.31 (m, 1H); 3.31-3.25 (m, 2H); 3.25-3.17 (m, 1H); 2.85-2.75 (m, 1H); 1.80-1.70 (m, 2H); 1.55-1.45 (m, 2H); 1.24-1.18 (m, 26H); 0.88 (t, J=7Hz, 3H). ^{31}P NMR ($CDCl_3$ + CD_3OD): δ 13.73.

8. Synthesis of Hexadecyloxypropyl- cidofovir (HDP-CDV)

The product from 7 above (0.38 g, 0.35 mmol) was added to 80% AcOH (10 mL) and stirred at 55 °C overnight. The solvent was evaporated and the residue was purified by column chromatography on silica gel (20% MeOH/CH_2Cl_2) to give 0.14 g of **hexadecyloxypropyl-cidofovir** (70% yield). ^1H NMR ($CDCl_3$): δ 7.72 (d, J=7Hz, 1H); 5.92 (d, J=8Hz, 1H); 4.16 (d, J=13Hz, 1H); 3.98-3.93 (m, 2H); 3.82-3.57 (m, 4H); 3.54-3.44 (m,4H); 3.40-3.38 (m, 2H); 1.90-1.86 (m, 2H); 1.56-1.53 (m, 2H); 1.29-1.21 (m, 26H); 0.88 (t, J=7Hz, 3H). ^{31}P NMR ($CDCl_3$): δ 20.99.

EXAMPLE 2: Synthesis of Hexadecyloxypropyl-adefovir, sodium salt (HDP-ADV)

Hydroxyethyladenine (2.15 g, 12 mmol) was suspended in dry N,N-DMF (25 mL) and sodium hydride (144, mg, 6mmol) was added and the mixture was stirred 15 min. To the mixture was added HDP-TsOMPA (1.0 g, 1.8 mmol) and stirring continued for 36 hours. The mixture was evaporated, then adsorbed on silica gel and purified by flash column chromatography. Product eluted with 35% MeOH/CH_2Cl_2. Pooled fractions were concentrated to give white solid hexadecyloxypropyl-adefovir as the sodium salt (0.44 g, 41% yield).

EXAMPLE 3. Synthesis of Octadecyloxyethyl-adefovir, sodium salt

1. Synthesis of toluenesulfonyloxymethylphosphonate, octadecyloxyethyl ester (ODE-TsOMPA)

Procedure of Example 1, step 6, was followed except that 2-octadecyloxy-1-ethanol was added. ^1H NMR: ($CDCl_3$) δ 0.87 (t, 3H), 1.33 (br s, 30H), 1.46

(m, 2H), 2.35 (s, 3H), 3.37 (t, 2H), 3.6 (s, 2H), 3.74 (t, 2H), 4.20 (t, 2H), 7.40 (d, 2H), 7.82 (d, 2H).

2. Synthesis of Octadecyloxy-adefovir, sodium salt

Hydroxyethyladenine (1.08 g, 6 mmol) was added to dry N,N-DMF (30 mL) and NaH (144, mg 6mmol) was added and stirred 15 min. To the mixture was added ODE-TsOMPA (1.05 g, 1.8 mmol) and stirring continued 36 hours. Solvent was evaporated and residue purified by flash column chromatography. Product eluted with 30-35% MeOH/CH_2Cl_2. Pooled fractions were concentrated to give white solid octadecyloxyethyl-adefovir (0.44 g, 41% yield).

EXAMPLE 4.: Synthesis of Hexadecyloxypropyl-(S)-HPMPA

1 Synthesis of N^6-$O^{3'}$-ditrityl- HDP-(S)-HPMPA

N6,O3'-ditrityl-(S)-dihydroxypropyladenine (9.2 g, 13.3 mmol) was dissolved in anhydrous trriethylamine (75 mL) with gentle heating, then NaH (3.7 g, 153 mmol) was added and the mixture stirred for 30 min under a nitrogen atmosphere. To the mixture was added a solution of HDP-TsOMPA (9.0 g, 15.4 mmol) in THF (25 mL). The mixture was heated to 60 °C and stirred for 48 hours. The mixture was then added to saturated NaCl/H_2O (100 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer, after drying over $MgSO_4$, was evaporated, and the residue purified by column chromatography on silica gel. Elution with 10% EtOH/CH_2Cl_2, followed by solvent evaporation, provided N^6-$O^{3'}$-ditrityl- HDP-(S)-HPMPA (5.5 g, 38% yield) as a thick oil. ^{1}H NMR: ($CDCl_3$) δ 0.89 (t, 3H), 1.33 (br s, 26H), 1.46 (m, 2H), 1.83 (p, 2H), 3.37-3.51 (m, 9H), 3.81-4.03 (m, 4H), 7.2 (br s, 30H), 7.80 (s, 1H), 8.20 (s, 1H).

2. Synthesis of Hexadecyloxypropyl-(S)-HPMPA

Product from step 1 above was treated with 80% aq acetic acid and heated to 50 °C for 2 hours. After evaporation of the solvent the product was recrystallized (EtOH) to afford hexadecyloxypropyl-(S)-HPMPA (82% yield). ^{1}H NMR: (DMSO-d_6) δ 0.83 (t, 3H), 1.21 (br s, 26H), 1.45 (m, 2H), 1.63 (pentet, 2H), 3.25-3.60 (m, 9H), 4.05-4.35 (m, 4H), 7.20 (s, 1H), 8.11 (s, 1H).

EXAMPLE 5. Synthesis of toluenesulfonyloxymethylphosphonate, oleyloxyethyl ester

Example 1, step 6 was followed except that 2-oleyloxy-1-ethanol was added. ^{1}H NMR: (CDCl3) δ 0.96 (t, 3H), 1.33 (br s, 22H), 1.46 (m, 2H), 1.96

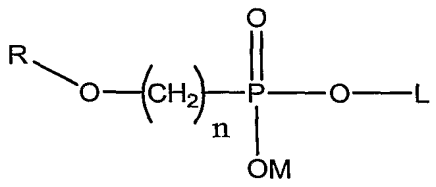
(m, 4H), 2.35 (s, 3H), 3.37 (t, 2H), 3.6 (s, 2H), 3.74 (t, 2H), 4.20 (t, 2H), 5.48 (m, 2H), 7.40 (d, 2H), 7.82 (d, 2H).

EXAMPLE 6. Synthesis of toluenesulfonyloxymethylphosphonate, oleyloxypropyl ester

Example 1, step 6 was followed except that 3-oleyloxy-1-propanol was added. ^{1}H NMR: (CDCl3) δ 0.96 (t, 3H), 1.33 (br s, 22H), 1.46 (m, 2H), 1.71 (p, 2H), 1.96 (m, 2H), 2.35 (s, 3H), 3.37 (t, 2H), 3.6 (s, 2H), 3.74 (t, 2H), 4.20 (t, 2H), 5.48 (m, 2H), 7.40 (d, 2H), 7.82 (d, 2H).

What is claimed is:

1. A process for making a lipophilic nucleoside phosphonate monoester of formula 3, including its stereoisomers,

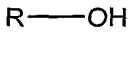


3

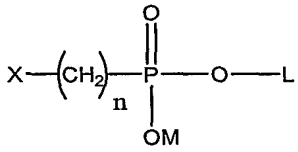
wherein the process comprises the steps of

a) providing compounds of formula 1 and formula 2;

b) reacting the compound of formula 1 and the compound of formula 2 in an aprotic solvent in presence of a strong base; and



2



1

c) isolating the compound of formula 3;

wherein M is –H, or a physiologically acceptable monovalent cation;

L is a lipophilic group; R is a nucleoside or a pharmaceutically acceptable derivative thereof; X is a leaving group; and n is 1 to 3.

2. The process of claim 1, wherein n is 1.

3. The process of claims 1 or 2, wherein the aprotic solvent is selected from DMF, THF and triethyamine.

4. The process of any of claims 1-3, wherein the solvent in DMF.

5. The process of any of claims 1-4, wherein the strong base is selected from sodium hydride, and potassium t-butoxide.

6. The process of any of claims 1-5, wherein X is selected from halogen, toluenesulfonyloxy, and methylsulfonyloxy.

7. The process of any of claims 1-6, wherein X bromo or iodo.

8. The process of any of claims 1-6, wherein X is toluenesulfonyloxy.

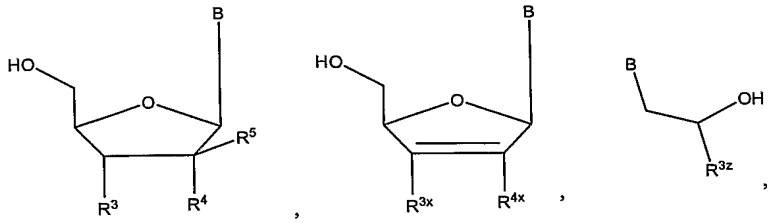
9. The process of any of claims 1-8, wherein M is –H, Na^+, K^+, or NH_4^+.

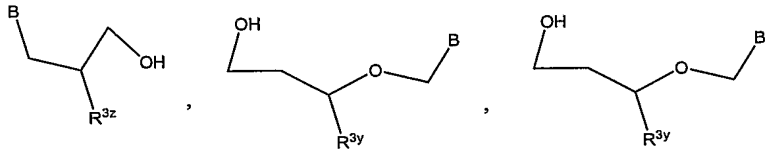
10. The process of any of claims 1-9, wherein M is –H or Na^+.

11. The process of any of claims 1-10, wherein M is –H.

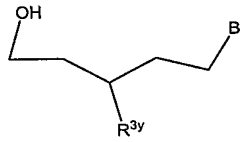
12. The process of any of claims 1-10, wherein M is Na^+.

13. The process of claim 1, wherein the compound of formula 2 has formula:





or



wherein

R^3, R^4 and R^5 are each independently H, hydroxy, halo, azido, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

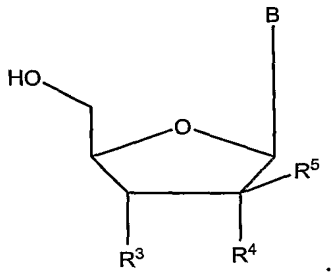
B is a purine or pyrimidine base or analog thereof;

R^{3x} is H, azido, substituted or unsubstitued C_{1-6} alkyl, substituted or unsubstitued C_{2-6} alkenyl or substituted or unsubstitued C_{2-6} alkynyl;

R^{4x} is H, C_{1-6} substituted or unsubstitued alkyl, C_{2-6} substituted or unsubstitued alkenyl or C_{2-6} substituted or unsubstitued alkynyl; and

R^{3z} is H, C_{1-6} alkyl, hydroxylC_{1-6} alkyl, haloC_{1-6} alkyl, azidoC_{1-6} alkyl or OH.

14. The process of claims 1 or 13, wherein the compound of formula 2 has formula:

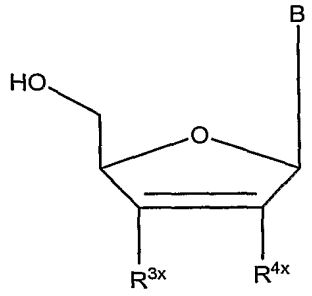


15. The process of claim 14, wherein R^3 is H, azido, substituted or unsubstitued C_{1-6} alkyl, substituted or unsubstitued C_{2-6} alkenyl or substituted or unsubstitued C_{2-6} alkynyl.

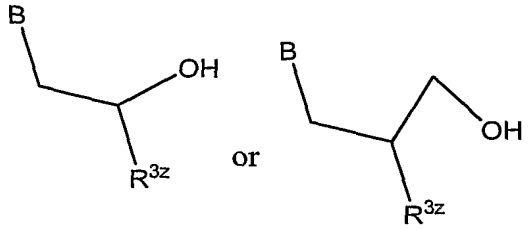
16. The process of claim 14 or 15, wherein R^3 is azido

17. The process of claim 14 or 15, wherein R^4 and R^5 are each independently selected from fluoro and hydroxymethyl.

18. The process of claim 13, wherein the compound of formula 2 has formula:



19. The process of claim 13, wherein the compound of formula 2 has formula:



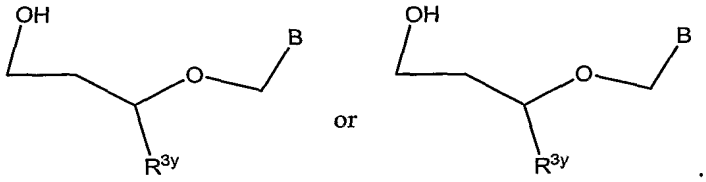
20. The process of claim 19, wherein R^{3z} is H, C_{1-6} alkyl, hydroxyl C_{1-6} alkyl, halo C_{1-6} alkyl, azido C_{1-6} alkyl or OH.

21. The process of claim 20, wherein R^{3z} is hydrogen C_{1-6}alkyl or hydroxyl C_{1-6} alkyl.

22. The process of claim 21, wherein R^{3z} is hydrogen, methyl or hydroxy methyl.

23. The process of claim 13, wherein R^{3z} is hydroxymethyl.

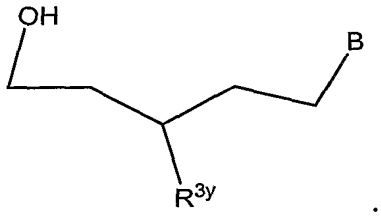
24. The process of claim 13, wherein the compound of formula 2 has formula:



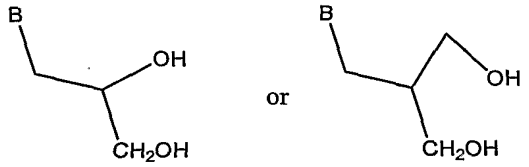
25. The process of claim 13 or 24, wherein R^{3y} is H, substituted or unsubstitued C_{1-6} alkyl, substituted or unsubstitued C_{2-6} alkenyl or substituted or unsubstitued C_{2-6} alkynyl; or OH.

26. The process of claim 24, wherein R^{3y} is hydrogen C_{1-6} alkyl or hydroxyl C_{1-6} alkyl.

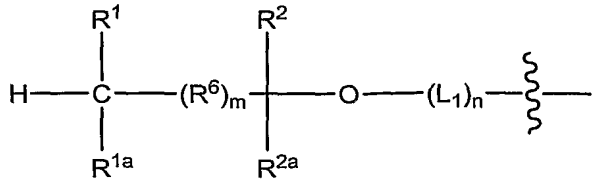
27. The process of claim 13, wherein the compound of formula 2 in the processes provided herein have formula:



28. The process of claim 13, wherein the compounds of formula 2 has formula:



29. The process of any of claims 1-28, wherein L is i) a substituted or unsubstituted C_8-C_{24} alkyl; ii) substituted or unsubstituted C_8-C_{24} alkenyl having from 1 to 6 double bonds, wherein substituents when present are selected from one or more halogen, alkyl, -OH, -SH, cycloalkyl, or epoxide; or iii) L has formula:

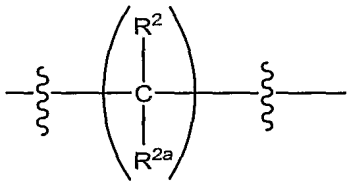


wherein:

R^1 and R^{1a} are independently –H, optionally substituted –O(C_1-C_{24})alkyl, -O(C_1-C_{24})alkenyl, -O(C_1-C_{24})acyl, -S(C_1-C_{24})alkyl, -S(C_1-C_{24})alkenyl, or –S(C_1-C_{24})acyl, wherein at least one of R^1 and R^{1a} are not –H, and wherein the alkenyl or acyl moieties optionally have 1 to 6 double bonds,

R^2 and R^{2a} are independently –H, optionally substituted-O(C_1-C_7)alkyl, -O(C_1-C_7)alkenyl, -S(C_1-C_7)alkyl, -S(C_1-C_7)alkenyl, -O(C_1-C_7)acyl, -S(C_1-C_7)acyl, -N(C_1-C_7)acyl, -NH(C_1-C_7)alkyl, -N((C_1-C_7)alkyl)$_2$, oxo, halogen, -NH_2, -OH, or –SH;

R^6, when present, is:



L_1 is a valence bond or a bifunctional linking molecule of the formula –J-(CR^7R^7)t-G-, wherein t is an integer from 1 to 24, J and G are independently –O-, -S-, -C(O)O-, or –NH-, and R^7 is –H, substituted or unsubstituted alkyl, or alkenyl;

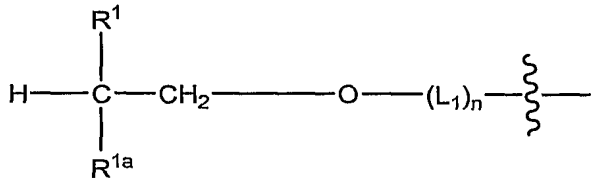
m is an integer from 0 to 6; and

n is 0 or 1.

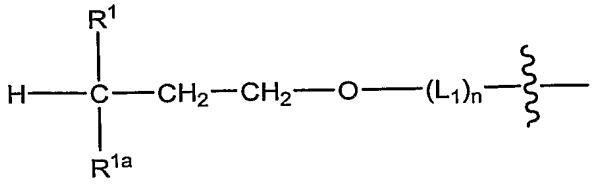
30. The process of claim 29, wherein m = 0, 1 or 2.

31. The process of any of claims 1-30, wherein n is 0 or 1.

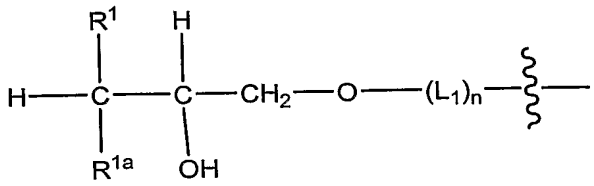
32. The process of any of claims 1-30, wherein L has formula:



33. The process of any of claims 1-30, wherein L has formula:



34. The process of any of claims 1-30, wherein L has formula:



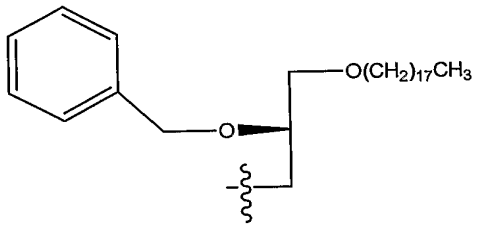
35. The process of any of claims 1-34, wherein R^1 is an alkoxy group having the formula $-O-(CH_2)_t-CH_3$ wherein t is 0-24.

36. The process of any of claims 1-29, wherein L has formula:

$CH_3(CH_2)_{15}O(CH_2)_3OH$; $CH_3(CH_2)_{17}O(CH_2)_2$-;

$CH_3(CH_2)_7CH=CH(CH_2)_8O(CH_2)_2$-; $CH_3(CH_2)_{15}$-;

$CH_3(CH_2)_7CH=CH(CH_2)_8O(CH_2)_3$-; and



37. The process of any of claims 1-30, wherein L is a C_{16}-C_{23} straight or branched chain alkyl.

38. The process of any of claims 1-30, wherein L is a C_{17}-C_{22} straight or branched chain alkyl.

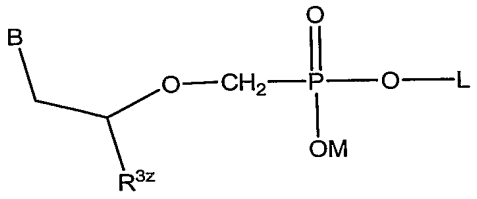
39. The process of any of claims 1-30, wherein L is substituted with one or more groups selected from lower alkyl and halo.

40. The process of claim 13, wherein B is selected from a natural or non natural purine or pyrimidine base.

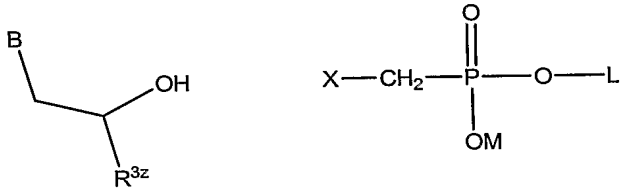
41. The process of any of claims 13 or 39, wherein B is selected from pyrimidin-1-yl, pyrimidin-3-yl, purin-3-yl, purin-7-yl or purin-9-yl residue.

42. The process of any of claims 13 or 39, wherein B is thymin-1-yl, cytosine-1-yl, adenine-9-yl or guanine-9-yl.

43. The process of claim 1, wherein the compound of formula 3 is



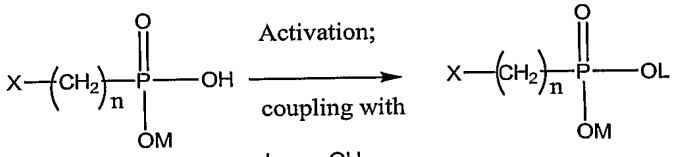
44. The process of claim 1, comprising the step of reacting a compound of formula **4** and a compound of formula **5** in presence of a strong base;



4 **5**

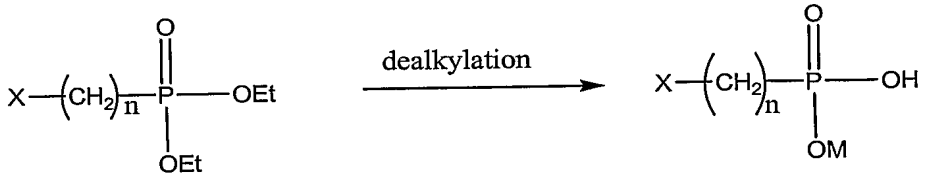
45. The process of claim 1, wherein the processes further comprises a step of preparing the methylene phosphonate lipophilic monoesters of formula 1.

46. The process of claim 1, wherein the processes further comprises a step of activation of a compound of formula 8 by reaction with an activating agent followed by coupling with a lipophilic alcohol of formula L-OH to produce a compound of formula 1:

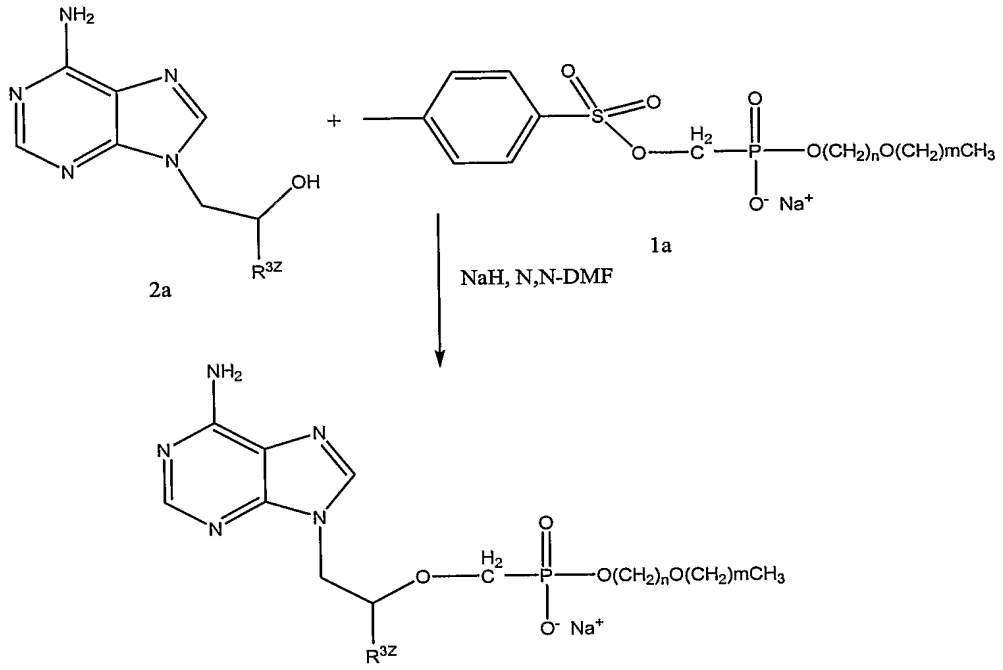


8 1

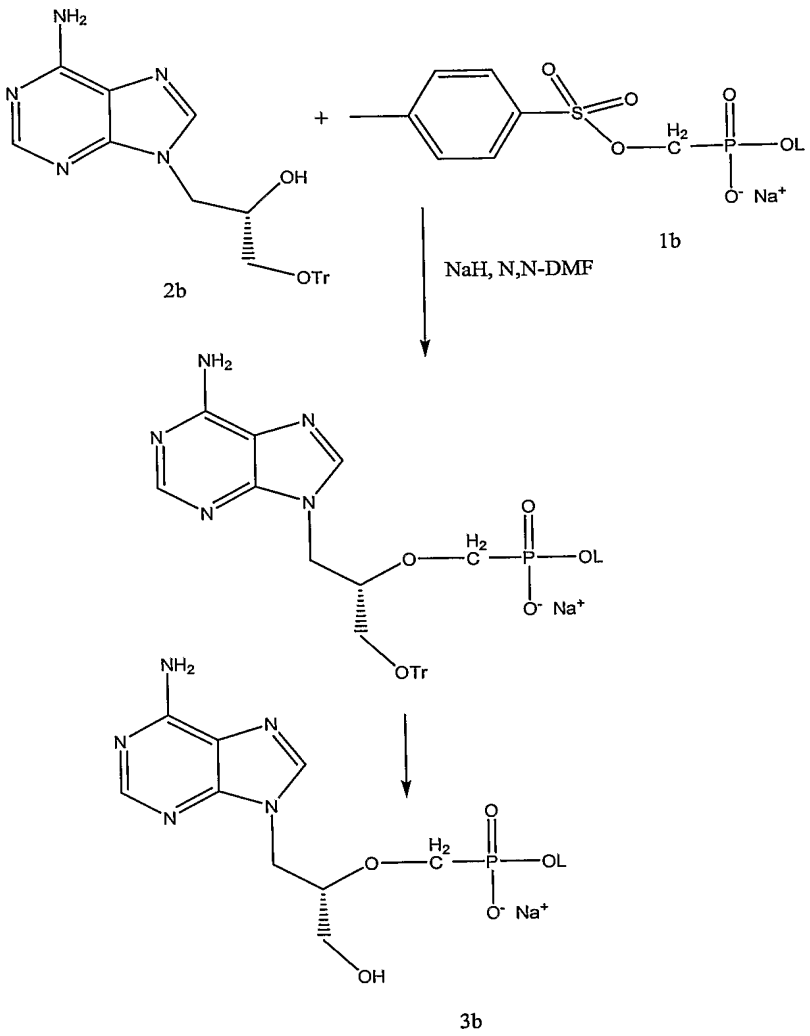
47. The process of claim 46, wherein the processes further comprises a step of dealkylating a diethyl ester of formula 9a to produce a compound of formula 8 as follows:



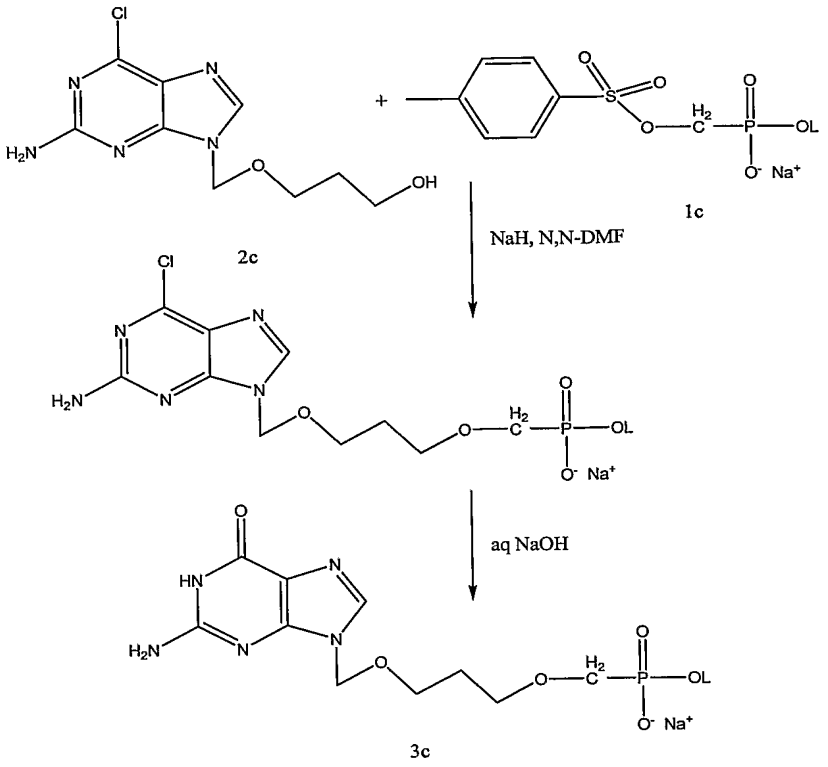
48. The process of claim 1, comprising a step of a) providing a compound of formula 2a and a compound of formula 1a; b) reacting the compound of formula 2a and the compound of formula 1a; and c) isolating a compound of formula 3a:



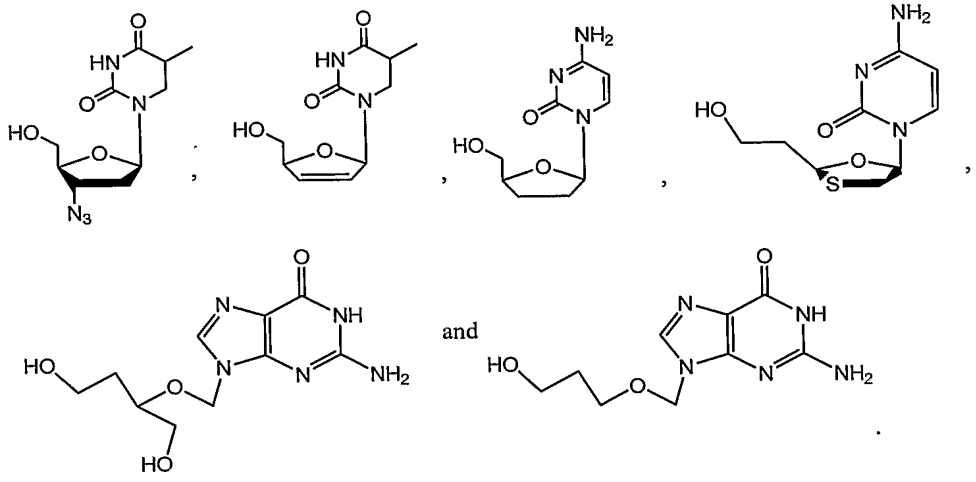
49. The process of claim 1, comprising: a) providing a compound of formula **2b** and a compound of formula **1b**; b) reacting the compound of formula **2b** and the compound of formula **1b**; and c) isolating a compound of formula **3b**:



50. The process of claim 1, comprising: a) providing a compound of formula **2c** and a compound of formula **1c**; b) reacting the compound of formula **2c** and the compound of formula **1c**; and c) isolating a compound of formula **3c**:



51. The process of claim 1, wherein the compound of formula 2 is selected from



52. The process of claim 1, wherein the compound of formula 3 is hexadecyloxypropyl-CDV.

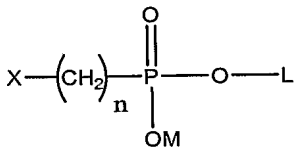
53. The process of claim 1, wherein the compound of formula 3 is hexadecyloxypropyl-PM-AZT.

54. The process of claim 1, wherein the compound of formula 3 is hexadecyloxypropyl-HPMPA.

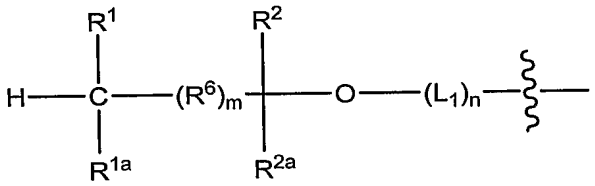
55. The process of claim 1, wherein the compound of formula 3 is hexadecyloxypropyl-adefovir.

56. The process of claim 1, wherein the compound of formula 3 is octadecyloxypropyl-adefovir.

57. A compound of formula:



wherein L is a substituted or unsubstituted C_8-C_{24} alkyl or substituted or unsubstituted C_8-C_{24} alkenyl having from 1 to 6 double bonds, wherein substituents when present are selected from one or more halogen, alkyl, -OH, -SH, cycloalkyl, or epoxide; or L has formula:

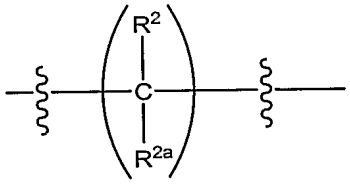


wherein:

R^1 and R^{1a} are independently –H, optionally substituted –O(C_1-C_{24})alkyl, -O(C_1-C_{24})alkenyl, -O(C_1-C_{24})acyl, -S(C_1-C_{24})alkyl, -S(C_1-C_{24})alkenyl, or –S(C_1-C_{24})acyl, wherein at least one of R^1 and R^{1a} are not –H, and wherein the alkenyl or acyl moieties optionally have 1 to 6 double bonds,

R^2 and R^{2a} are independently –H, optionally substituted-O(C_1-C_7)alkyl, -O(C_1-C_7)alkenyl, -S(C_1-C_7)alkyl, -S(C_1-C_7)alkenyl, -O(C_1-C_7)acyl, -S(C_1-C_7)acyl, -N(C_1-C_7)acyl, -NH(C_1-C_7)alkyl, -N((C_1-C_7)alkyl)$_2$, oxo, halogen, -NH_2, -OH, or –SH;

R^6, when present, is:



L_1 is a valence bond or a bifunctional linking molecule of the formula –J-(CR^7R^7)t-G-, wherein t is an integer from 1 to 24, J and G are independently –O-, -S-, -C(O)O-, or –NH-, and R^7 is –H, substituted or unsubstituted alkyl, or alkenyl;

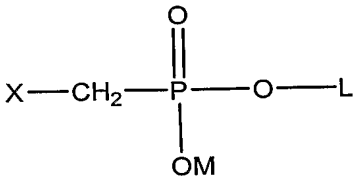
m is an integer from 0 to 6;

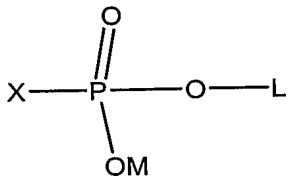
n is 1 to 3;

X is a leaving group; and

M is –H, or a physiologically acceptable monovalent cation.

58. The compound of claim 57, wherein the compound has formula:



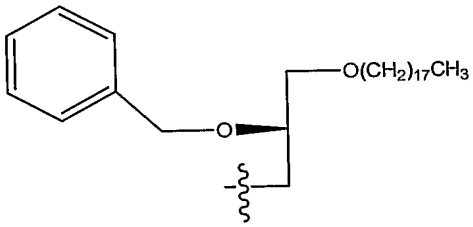
or


59. The compound of claims 57 or 58, wherein L has formula:

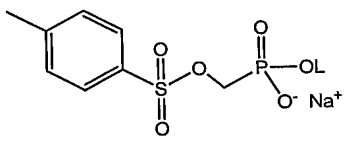
$CH_3(CH_2)_{15}O(CH_2)_3OH$; $CH_3(CH_2)_{17}O(CH_2)_2$-;

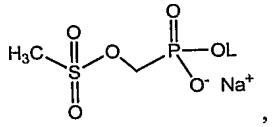
$CH_3(CH_2)_7CH{=}CH(CH_2)_8O(CH_2)_2$-; $CH_3(CH_2)_{15}$-;

$CH_3(CH_2)_7CH{=}CH(CH_2)_8O(CH_2)_3$-; and



60. The compound of claim 57, wherein the compound has formula:



,


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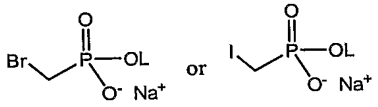
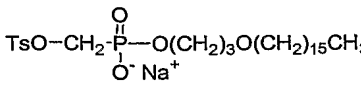


or

61. The compound of claim 57, wherein the compound has formula:



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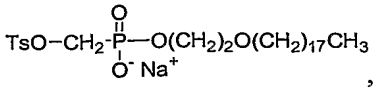

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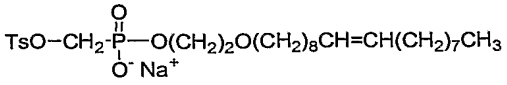
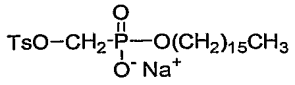


,


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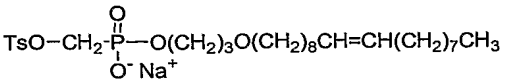
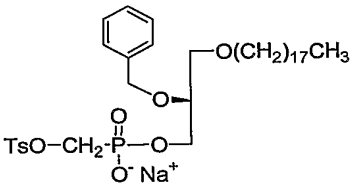


and



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62. A compound selected from N^4-monomethoxytrityl-$O^{3'}$-(trityl)-dihydroxypropylcytosine and N^4,$O^{3'}$-ditrityl-dihydroxypropylcytosine.